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# **THE LEGAL ORIGINS OF THE NEW ENGLAND COMPOUNDING CENTER CRISIS AND THE FUTURE OF DRUG COMPOUNDING REGULATION**

**Leo R. Takaoka, David P. M. Pleyne, and Marc A. Rodwin.\***

## **ABSTRACT**

The outbreak of fungal meningitis in 2012 that injured more than 750 people involved more than misconduct by the New England Compounding Center (NECC). It was due to the unclear legal status of compounding pharmacies, problems with the legal oversight, limited FDA authority, and overlapping and unclear federal and state jurisdiction. These conditions became hazardous when compounding pharmacies assumed functions that went beyond traditional compounding. This article explores the legal origins of the NECC crisis. It also examines how the state and federal government have responded, and it assesses the legislation enacted in 2013.

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\* Leo R. Takaoka, Ph.D., J.D., Technical Specialist, McCarter & English, LLP; David P. M. Pleyne, Ph.D., J.D., Director of Chemistry IP and Patent Counsel, ImmunoGen, Inc.; Marc A. Rodwin, J.D., Ph.D., Professor, Suffolk University Law School and 2017-18 Chair in Integrated Cancer Research (jointly with SIRIC) Fondation IMéRA - Aix Marseille Université. Authors are grateful to Lael L. Cheung, Ph.D., for laboriously reviewing draft iterations of this manuscript.

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I.	Introduction .....	3
II.	Compounding Pharmacy in American Medicine .....	5
III.	Federal Oversight of Compounding Pharmacies .....	9
	A. Before the Food and Drug Modernization Act of 1997 .....	9
	B. The FDA Modernization Act § 503A Regulates Compounding, But Ninth Circuit Strikes It Down Because It Includes Unconstitutional Advertising Restrictions .....	16
	C. The Fifth Circuit Upholds § 503A except its Advertising Restrictions .....	19
	D. FDA Oversight After the Circuit Split.....	20
IV.	Obstacles to FDA Oversight and Calls for Greater FDA Regulation of Drug Compounding .....	23
	A. Limited FDA Inspection Authority .....	24
	B. The FDA’s Limited Access to Relevant Information.....	25
	C. Drug Manufacturers Pressure the FDA to Act Against Compounding Pharmacies .....	27
	1. Wyeth’s Citizen Petition .....	27
	2. KV Pharmaceutical Suit against the FDA.....	29
V.	The New England Compounding Center Crisis .....	30
	A. FDA Oversight of NECC .....	30
	B. FDA Oversight of Ameridose.....	35
	C. NECC Violates Legal and Quality Standards.....	39
VI.	State Response to the Crisis.....	41
	A. Hobbled State Oversight.....	41
	B. States’ Response After the Fungal Meningitis Outbreak ...	42
VII.	The Drug Quality and Security Act of 2013.....	44
	A. The Compounding Quality Act .....	46
	1. Outsourcing Facilities for Certain Non-Traditional Compounding.....	46
	2. Labeling, Good Manufacturing Practices, Reporting Requirements, and Inspections.....	49
	3. Traditional Compounding .....	50
	4. Federal and State Coordination and Communication ...	52
	B. The Drug Supply Chain Security Act (DSCA).....	53
VIII.	Key Unresolved Issues .....	54
	A. The Legal Status of Compounding Pharmacies Under Federal Law .....	54
	B. Conflicting Standards within Federal Law and Between Federal and State Law .....	55

### I. Introduction

In 2012, an outbreak of fungal meningitis and other persistent fungal infections<sup>1</sup> both sickened more than 750 people and resulted in sixty-four deaths in twenty states, events that became known as the New England Compounding Center Crisis (NECC). Investigations revealed that the victims had been exposed to contaminated products compounded and distributed by NECC, a licensed pharmacy located in Framingham, Massachusetts, which was owned and managed by the same individuals who owned and managed Ameridose, a pharmaceutical manufacturer that also faced quality assurance problems that endangered patients.<sup>2</sup> The NECC outbreak ranks as one of the worst public health crises associated with contaminated drugs in the history of the United States, and it exposed fundamental failures in drug safety oversight.<sup>3</sup> It illustrates the problems that can occur when pharmacies go beyond traditional drug compounding and produce large quantities of drugs without patient-specific prescriptions, and sell the drugs to health facilities in multiple states.<sup>4</sup> In effect, these pharmacies manufacture drugs under the guise of drug compounding, thereby eluding the safety and effectiveness requirements under the 1938 Federal Food, Drug, and Cosmetics Act (FDCA).

Starting in the summer of 2012, NECC shipped over 17,000 contaminated vials of an injectable steroid solution into multiple states.<sup>5</sup> The medication was often injected into the spinal columns of patients to relieve chronic pain. In September 2012, physicians at Vanderbilt University reported a case of fungal meningitis in a patient who had received

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<sup>1</sup> Pontikes, R. G.; Gallagher, P. C.; Hart, E. L. *The Regulation of Pharmacy Compounding: FDA Authority and the Compounding Quality Act of 2013*, Food and Drug Law Institute, Washington, DC, 2014 [hereinafter Pontikes] (finding the states most affected by NECC's contaminated compounded drugs were Michigan, with 264 patients infected and nineteen deaths, and Tennessee, with fifteen patients infected and sixteen deaths).

<sup>2</sup> Committee on Energy and Commerce, 113<sup>th</sup> Cong. FDA'S OVERSIGHT OF NECC AND AMERIDOSE: A HISTORY OF MISSED OPPORTUNITIES? (2013), <http://docs.house.gov/meetings/IF/IF02/20130416/100668/HHRG-113-IF02-20130416-SD101.pdf> [hereinafter NECC AND AMERIDOSE].

<sup>3</sup> NECC AND AMERIDOSE, *supra* note 2, at 1.

<sup>4</sup> According to the U.S. Centers for Disease Control and Prevention, as of July 1, 2013, 749 individuals who received the contaminated steroid injections became ill with fungal meningitis or other types of infections and sixty-one of them have died. NECC AND AMERIDOSE, *supra* note 2, at 1.

<sup>5</sup> NECC AND AMERIDOSE, *supra* note 2, at 1.

an injection of the compounded steroid methylprednisolone.<sup>6</sup> Five additional complaints, also in Tennessee, were identified a few days later. All six cases were traced to methylprednisolone sterile injections compounded by NECC, which compelled the Tennessee Department of Health to contact the Massachusetts Department of Public Health (MDPH).<sup>7</sup> Soon thereafter, Massachusetts conducted an on-site inspection of the NECC facilities, but NECC voluntarily recalled only three lots of the methylprednisolone sterile injections.<sup>8</sup> A week later, officials from the Food and Drug Administration (FDA) were on site, at which time NECC voluntarily recalled all of its compounded products and surrendered its Massachusetts pharmacy license.<sup>9</sup>

FDA inspection of the NECC facility revealed that every vial of methylprednisolone that was tested contained microbial growth, with one vial even showing evidence of fungus.<sup>10</sup> Despite NECC representing that the raw materials used for its injectable preparations were sterile, the FDA alleged that NECC used non-sterile active pharmaceutical ingredients (APIs) and raw materials for its injectable products.<sup>11</sup> Further tests showed bacterial and mold growth throughout the NECC facility, including in and on the surfaces of clean rooms, in gown rooms, on the tables and near the hoods where the drugs were compounded.

The NECC compounding crisis was a long time coming. It arose not only from the misconduct of one compounding center, but also from problems with legal oversight, weaknesses in federal legislation that limited the FDA's authority owed to overlapping and unclear federal and state jurisdiction, and the unclear legal status of compounding pharmacies. These conditions became critical when changes in the marketing of drugs allowed compounding pharmacies to take on functions that went beyond traditional compounding. This article explores the legal origins of the NECC crisis. It also examines how the state and federal government have responded, and it assesses the legislation that Congress enacted in 2013.

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<sup>6</sup> Kevin Outterson, *Regulating Compounding Pharmacies after NECC*, 367 NEW. ENG. J. MED. 1969, 1971 (2012); see Pontikes, *supra* note 1.

<sup>7</sup> Outterson, *supra* note 6; see Pontikes, *supra* note 1.

<sup>8</sup> Outterson, *supra* note 6; see Pontikes, *supra* note 1.

<sup>9</sup> FDA Form 483 issued to New England Compounding Center on November 26, 2012. Pontikes, *supra* note 1; see Outterson, *supra* note 6.

<sup>10</sup> Pontikes, *supra* note 1.

<sup>11</sup> Pontikes, *supra* note 1.

## II. *Compounding Pharmacy in American Medicine*

Drug compounding comprises the process of combining, mixing, or altering ingredients to create a drug. Traditionally, drug compounding intended to create a drug tailored to the needs of an individual patient in response to a licensed medical practitioner's prescription.<sup>12</sup> Now, drug compounding also encompasses creating a drug without a prescription, based on order history – a practice known as anticipatory compounding.<sup>13</sup> According to estimates, between thirty million to forty million prescriptions are compounded annually, comprising approximately one to three percent of the prescription drug market.<sup>14</sup> Nevertheless, despite its small market share, pharmacy compounding plays an important role because it can provide a medication in a form better suited to the needs of an individual patient, e.g., by removing or replacing an excipient to which the patient is allergic or providing a liquid form of a tableted drug for a child who cannot swallow a tablet.<sup>15</sup>

Traditionally, the states have regulated compounding pharmacies.<sup>16</sup> Over time, the activities of compounding pharmacies have expanded and some compounding pharmacies engage in activities that lie outside their traditional practice.<sup>17</sup> In the 1990s and early 2000s, some compounding pharmacies started to resemble drug manufacturers.<sup>18</sup> The FDA tried to respond to these changes but was hampered due to limited jurisdiction and challenges to its regulatory authority.<sup>19</sup>

Under the FDCA, compounded drugs are considered “new drugs,”<sup>20</sup> and are subject to FDA rules regarding manufacturing and market approval. However, traditional compounding pharmacies cannot

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<sup>12</sup> U.S. GOV'T ACCOUNTABILITY OFF., GAO-13-702, DRUG COMPOUNDING: CLEAR AUTHORITY AND MORE RELIABLE DATA NEEDED TO STRENGTHEN FDA OVERSIGHT (2013) [hereinafter GAO REPORT].

<sup>13</sup> GAO REPORT, *supra* note 12, at 5.

<sup>14</sup> Amanda Phillips, *The Role of Compounding in Tomorrow's Care of Patients: Personalized Pharmaceutical Care*, INT'L ACAD. OF COMPOUNDING PHARMACISTS (2011), <http://www.iacprx.org/displaycommon.cfm?an=1&subarticlenbr=1>; see Pontikes, *supra* note 1.

<sup>15</sup> GAO REPORT, *supra* note 12, at 4.

<sup>16</sup> Pontikes, *supra* note 1.

<sup>17</sup> Pontikes, *supra* note 1.

<sup>18</sup> Pontikes, *supra* note 1.

<sup>19</sup> Pontikes, *supra* note 1.

<sup>20</sup> The FDCA defines “new drug” as “[a]ny drug . . . the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof . . . .” 21 U.S.C. § 321(p)(1) (2017). Drug manufacturers submit new drug applications (NDAs) to the FDA to seek

practically seek regulatory approval for each individualized drug that is compounded.<sup>21</sup> As a result, the FDCA exempts compounding pharmacies from many of the stringent requirements imposed upon traditional drug manufacturers.<sup>22</sup>

Free from the burden imposed on large-scale drug manufacturing under the FDCA, compounding pharmacies can sometimes sell medications at a lower price. The NECC crisis reflects an evolution to new business models that expand a pharmacist's role in patient care.<sup>23</sup> Healthcare providers such as hospitals or doctors' offices, sometimes, procured drugs from cheaper compounders rather than from manufacturers.

Prior to the NECC crisis, many pharmacies thought certain activities fell under FDA jurisdiction, and states generally believed that the FDA lacked the authority to regulate traditional compounding pharmacies. A split between the Fifth and Ninth Circuit Court of Appeals undermined the FDA's mandate, leaving the FDA hesitant to use its enforcement powers. This state of affairs created a false sense of security regarding compounded drugs and a dangerous situation for consumers. This NECC crisis paved the way for the Drug Quality and Security Act (DQSA), passed on November 27, 2013, providing the FDA more authority to regulate and monitor the manufacturing of compounded drugs.

Because some patients have a clinical need that cannot be met with existing pharmaceutical products, compounding pharmacies provide an important service to those patients. The growth in interest of customized products, including allergen-free drugs, single administration of multiple drugs, and individualized formulations of drugs (such as liquids instead of tablets) plays a major role in heightened demand for compounded drugs.<sup>24</sup> In addition, drug compounders also help supply

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approval to market and sell new pharmaceutical drug products in the United States. 21 U.S.C. § 321(p) (2017). In addition, abbreviated new drug applications (ANDAs) are submitted to FDA to seek approval to market a generic version of a drug after the period of exclusivity and any patents for a brand-name drug expire. *Id.*

<sup>21</sup> Pontikes, *supra* note 1.

<sup>22</sup> Pontikes, *supra* note 1.

<sup>23</sup> See, e.g., Russell Redman, *2012 Retail Forecast: Chain Drug Eyes Broader Role*, CHAIN DRUG REVIEW (Dec. 29, 2011), <http://www.chaindrugreview.com/2012-retail-forecast-chain-drug-eyes-broader-role>; Council on Credentialing in Pharmacy, *Scope of Contemporary Pharmacy Practice: Roles, Responsibilities, and Functions of Pharmacists and Pharmacy Technicians*, J. AM. PHARM. ASS'N. 24 (2010).

<sup>24</sup> Carolyn Y. Johnson, *Compounding Pharmacies Fill Important Medical Niche*, BOSTON

medications that are produced by manufacturing firms when in short supply. Shortages of commercially-available drugs, especially shortages of generic sterile products, play a central role in the increased demand for drug compounding.<sup>25</sup>

Pharmacists compound drugs using a variety of techniques, including compounding from bulk substances or APIs, which are generally defined as substances used in the manufacturing, processing or packaging of a drug which become a finished dosage form of the drug.<sup>26</sup> Compounded drugs fall into two categories: 1) sterile preparations, including intravenously administered fluids and injectable drugs, which pose special risks of contamination and require special safeguards to prevent injury or death; and 2) non-sterile preparations such as capsules, ointments, creams, gels, suppositories, and pills, which are considered to have lower production risk.<sup>27</sup>

Drug compounding is a traditional component of the pharmacy profession,<sup>28</sup> and is practiced in hospital pharmacies, in community pharmacies, in chain drug store pharmacies, and in home infusion settings.<sup>29</sup> In 2012, nearly half of the 56,000 community-based pharmacies in the United States performed some type of compounding.<sup>30</sup> Precise statistics on the prevalence of pharmacies that compound drugs are beyond the scope of this article. However, there are also approximately 3,000 community-based pharmacies that specialize in the compounding of sterile

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GLOBE (Nov. 3, 2012), <https://www.bostonglobe.com/metro/2012/11/02/compounding-pharmacies-filled-niche-for-major-hospitals/47MsPtBMEkT67TQmfNXF8O/story.html>.

<sup>25</sup> *Id.*; Kristina Fiore, *Drug Shortages Spark Use of Compounders*, MEDPAGE TODAY (Oct. 18, 2012), <http://www.medpagetoday.com/meetingcoverage/asa/35406>; T. Meyer, *Overseeing Outsourced Compounding During Shortages*, *Pharmacy Purchasing and Products*, PHARMACY PURCHASING & PRODUCTS (June 2012), [http://www.pppmag.com/article/1141/June\\_2012/Overseeing\\_Outsourced\\_Compounding\\_during\\_Shortages/#.T9k83KBsI1Q](http://www.pppmag.com/article/1141/June_2012/Overseeing_Outsourced_Compounding_during_Shortages/#.T9k83KBsI1Q) blogger; Katie Thomas, *Lapses at Big Drug Factories Add to Shortages and Danger*, N.Y. TIMES (Oct. 17, 2012), <http://www.nytimes.com/2012/10/18/business/drug-makers-stalled-in-a-cycle-of-quality-lapses-and-shortages.html>.

<sup>26</sup> 21 C.F.R. § 207.3(a)(4)(2017); *see also* 21 C.F.R. § 207.1(b)(2017).

<sup>27</sup> U.S. PHARMACOPEIAL CONVENTION, (795) PHARMACEUTICAL COMPOUNDING – NON-STERILE PREPARATIONS 1 (2014); *see also* Letter from Stuart Wright, Deputy Inspector Gen. for Evaluation and Inspections, to Dr. Margaret A. Hamburg, Comm’r of Food and Drugs (Apr. 10, 2013), <http://oig.hhs.gov/oei/reports/oei-01-13-00150.pdf> [hereinafter *OIG Memorandum*].

<sup>28</sup> *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 361 (2002); *Med. Ctr. Pharmacy v. Mukasey*, 536 F.3d 383, 388 (5th Cir. 2008).

<sup>29</sup> GAO REPORT, *supra* note 12, at 5.

<sup>30</sup> *Public Hearing into Alleged Violations of Pharmacy Regulations at the New England Compounding Center and Associated Issues Concerning Oversight Capabilities at the Department of Public Health*, Mass. H.R.. 3 (2012).

and non-sterile prescription drugs.<sup>31</sup> Up to 26,000 community-based pharmacies engage in some form of compounding and 7500 specialize specifically in compounding.<sup>32</sup> A 2013 report prepared for the FDA by the U.S. Department of Health and Human Services Office of the Inspector General revealed that 92 percent of acute-care hospitals surveyed used sterile compounded drugs administered via injection or infusion.<sup>33</sup> Of those acute-care hospitals, 85 percent outsourced at least some of the compounded drug products from extramural pharmacies.<sup>34</sup>

The FDA regulates commercial pharmaceutical manufacturing activities. However, the states are the primary regulators of pharmacies and the practice of compounding. State laws generally require compounding pharmacies to receive a prescription order from a medical practitioner for an individually identified patient or a patient-specific prescription, before a drug can be compounded and sold.<sup>35</sup> Some states allow drugs to be compounded pursuant to a healthcare provider's order, in anticipation for use at the office.<sup>36</sup> The "office use" compounded drug can then be administered directly to a visiting patient at the provider's office.<sup>37</sup>

State pharmacy laws typically require registration and licensing for pharmacies and pharmacists.<sup>38</sup> They also establish labeling and purity requirements for compounded drugs, and they set training and education

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<sup>31</sup> GAO REPORT, *supra* note 12, at 5.

<sup>32</sup> GAO REPORT, *supra* note 12, at 5.

<sup>33</sup> The hospitals reported that drug shortages of commercially available products was "a very important factor when deciding whether to outsource" compounded sterile drugs. OIG Memorandum, *supra* note 27, at 6. The OIG went on to describe that "[a]ccording to pharmacists with whom we spoke, [compounded drugs] prepared onsite often have limited shelf lives or must be refrigerated." *Id.* "In many cases, outside pharmacies can provide products that have undergone stability testing and have extended shelf lives." *Id.* "Outsourcing these CSPs enables hospitals to have product on hand when needed with less waste." *Id.*; Pontikes, *supra* note 1.

<sup>34</sup> Pontikes, *supra* note 1.

<sup>35</sup> "A prescription shall be compounded and dispensed only pursuant to a specific order for an individual patient issued by a prescriber. A limited quantity may be compounded in anticipation of prescription drug orders based on routine, regularly observed prescribing patterns." Ohio Admin. Code. Ann. § 4729-9-21(F) (repealed 2016).

<sup>36</sup> Compounding nonprescription drugs, however, would violate section 503A of the FDCA, since the compounded nonprescription drug would be misbranded, adulterated, and a new drug. Federal Food, Drug, and Cosmetic Act (FDCA) § 503(A) (2016); *see* Houck v. Iowa Bd. of Pharmacy Examiners, 752 N.W.2d 114 (Iowa 2008).

<sup>37</sup> "Nothing in this act is meant to limit a prescriber's ability under pre-existing law to order a compounded medication for use in the prescriber's practice, as permitted by State and federal law." N.J.S.A. § 45:14-41 (2000).

<sup>38</sup> N.Y. Educ. Law § 6803 (McKinney 2016).

requirements for compounding pharmacists.<sup>39</sup> State Pharmacy Boards oversee and enforce pharmacy compounding practices.<sup>40</sup> States typically require that pharmacists comply with United States Pharmacopeia (USP) and National Formulary (NF) standards.<sup>41</sup> These standards are also incorporated into Federal law by the FDCA.<sup>42</sup>

Under the FDCA, any drug that does not comply with federal quality standards violates the Act; there is no exception for compounded drugs. However, section 510(g) of the FDCA recognizes that traditional compounding by pharmacists, as regulated by state law, is not considered manufacturing and therefore exempts pharmacies from registering as manufacturers if they do not manufacture, prepare, propagate, compound, or process drugs or devices for sale other than in the regular course of dispensing or selling drugs or devices at retail.<sup>43</sup>

### III. Federal Oversight of Compounding Pharmacies

#### A. Before the Food and Drug Modernization Act of 1997

In 1906, Congress enacted the Pure Food and Drug Act to improve drug safety. The Act targeted false labeling of drugs but did not attempt to regulate the practice of drug compounding, which was traditionally a

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<sup>39</sup> See, e.g., *id.*; Ga. Code Ann. § 26-3-7 (2017).

<sup>40</sup> See *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 361 (2002); *Med. Ctr. Pharmacy v. Mukasey*, 536 F.3d 383, 388 (5th Cir. 2008). *United States v. Franck's Lab, Inc.*, 816 F. Supp. 2d 1209, 1216 (M.D. Fla. 2011) (“Because the practice of pharmacy is state-governed, the states, including Florida, regulate compounding as part of their regulation of pharmacists.”); see, e.g., CALIFORNIA STATE BOARD OF PHARMACY, <http://www.pharmacy.ca.gov> (last visited Feb. 23, 2018); FLORIDA BOARD OF PHARMACY, <http://www.floridaspharmacy.gov> (last visited Feb. 23, 2018); TEXAS STATE BOARD OF PHARMACY, <http://www.tsbp.state.tx.us/> (last visited Feb. 23, 2018).

<sup>41</sup> The USP and the NF are two compendia that set compounding standards that widely acknowledge scientifically sound procedures and best practices for the compounding of drugs, and that facilitate the delivery of consistent and good-quality compounding of drugs to patients. GAO REPORT, *supra* note 12. The USP and NF also provide monographs for drug articles, including ingredients used in compounded preparations, and monographs for the compounded preparations themselves, comprising standards of identity, quality, purity, strength, packaging, and labeling. *Id.*; see FDCA § 201(j) (2016) (designating the USP as the “official compendium” of the FDCA); U.S. PHARMACOPEIAL CONVENTION, (795), *supra* note 27 (defining “non-sterile drug compounding”); U.S. PHARMACOPEIAL CONVENTION, (797) PHARMACEUTICAL COMPOUNDING—STERILE PREPARATIONS 1 (2015) (defining “sterile drug compounding”).

<sup>42</sup> Section 503A of the FDCA requires that drug products be compounded in compliance with USP Chapter 797 standards, if they are available. FDCA § 503(A) (2016). Many states require compounded drugs to comply with the USP and NF standards. See GAO REPORT, *supra* note 12, at 14.

<sup>43</sup> 21 U.S.C. § 360(g) (2017).

state function.<sup>44</sup> As long as a drug compounder made no false or misleading claims regarding the ingredients, they did not violate the statute.<sup>45</sup>

The Pure Food and Drug Act established federal authority to interdict and penalize the interstate marketing of any drug that was adulterated or misbranded.<sup>46</sup> The FDCA, together with the 1962 Kefauver-Harris Drug Amendments to the FDCA, form the core of modern drug law in the United States.<sup>47</sup> The FDCA made the FDA a gate-keeper whose approval was necessary prior to the marketing of new drugs. The FDCA empowered the FDA to set official standards for strength, quality, purity, packaging, and labeling, to regulate the manufacture, marketing, and distribution of pharmaceutical products, and to enforce the Act.<sup>48</sup> Initially the FDA only reviewed drugs to ensure that they were not unsafe. The 1962 Amendments prohibited the marketing of new drugs if their sponsors failed to convince the FDA that the drugs were effective as well as safe.<sup>49</sup> While the FDCA does not explicitly regulate drug compounding, the statute does regulate the introduction of new drugs, as well as misbranding of drugs, adulteration of drugs, and production and distribution. The FDA has applied these standards to compounded drugs.<sup>50</sup>

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<sup>44</sup> Federal Food and Drug Act of 1906, Pub. L. 59-384, 21 U.S.C. Sec 1-15 (1906); *Joint Session of Am. Pharm. Ass'n, et al.*, 17 J. AM. PHARM. ASS'N 1000, 1010-13 (1938); *United States v. Antikamnia Chem. Co.*, 231 U.S. 654, 665 (1913); see also ANDREW NOLAN, FEDERAL AUTHORITY TO REGULATE THE COMPOUNDING OF HUMAN DRUGS, CRS REPORT R43038 at 13 (2013) [hereinafter CRS REPORT R43038].

<sup>45</sup> JAMES HARVEY YOUNG, THE TOADSTOOL MILLIONAIRES: A SOCIAL HISTORY OF PATENT MEDICINES IN AMERICA BEFORE FEDERAL REGULATION 9, 243-44 (1961); see also CRS REPORT R43038, *supra* note 44, at 2.

<sup>46</sup> Section 7 of the 1906 Act deemed a drug “adulterated” when: 1) it differs from the standard of strength, quality, or purity as determined by the test established by the USP or NF office and 2) the strength or purity falls below the professed standard or quality under which it is sold. Pure Food and Drug Act of 1906, Pub. L. No. 59-384, 34 Stat. 768 (1906). Under section 8, a drug is “misbranded” if: 1) the drug is an imitation of or offered for sale under the name of another drug; 2) the terms of weight or measure are not correctly stated on the outside of the package; and 3) either (a) the label bears any false or misleading statements, or (b) the original package has been removed, or if the package fails to bear a statement on the label of the quantity or proportion of any alcohol, morphine, opium, cocaine, heroin, alpha or beta eucaine, chloroform, cannabis indica, chloral hydrate, or acetanilide, or any derivative or preparation of such substances contained. *Id.*

<sup>47</sup> John C. Krantz Jr., *New Drugs and the Kefauver-Harris Amendment*, J. NEW DRUGS, Mar-Apr. 1966, at 77; Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780.

<sup>48</sup> FDCA § 1003; 21 U.S.C. § 393 (2017); see, e.g., SUSAN THAUL, HOW FDA APPROVES DRUGS AND REGULATES THEIR SAFETY AND EFFECTIVENESS, CONG. RESEARCH SERV., R41983, at 4-5 (2013); see also CRS REPORT R43038, *supra* note 44, at 4.

<sup>49</sup> CRS REPORT R43038, *supra* note 44, at 3.

<sup>50</sup> CRS REPORT R43038, *supra* note 44, at 3.

Since 1938, the FDCA has regulated the introduction of new drugs. Specifically, section 201(p) of the FDCA defines a “new drug” as any drug that is not “generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof.”<sup>51</sup> To receive FDA approval, sponsors must submit data from well controlled studies that the FDA finds the drugs are “safe and effective” for their intended use prior to the products being marketed to the public, and transported or distributed in interstate commerce.<sup>52</sup> The Act sets rules for testing new drugs under the Investigational New Drug (IND) program.<sup>53</sup> The process by which the FDA reviews evidence that a sponsor submits when seeking permission to market a new drug, is referred to as the New Drug Application (NDA) protocol.<sup>54</sup> Drug manufacturers must also ensure that its manufacturing site passes FDA Current Good Manufacturing Practices (cGMPs) inspection for production and packaging,<sup>55</sup> and obtain FDA approval for the drug’s labeling.<sup>56</sup>

Section 502 of the FDCA prohibits misbranding.<sup>57</sup> The term “misbranding” applies to false or misleading information or packaging, lack of required information, lack of clear or conspicuous information, and improper or deficient packaging and labeling.<sup>58</sup> Section 502 also deems a drug misbranded if the labeling does not contain adequate direction for use.<sup>59</sup> Generally, “Adequate Direction for Use” means directions under

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<sup>51</sup> FDCA § 201(p)(1); *see* FDCA § 201(g)(1) (defining “drug” as a substance recognized by an official pharmacopeia or formulary that is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease).

<sup>52</sup> “No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application [by the FDA] is effective with respect to such drug.” FDCA § 505(a).

<sup>53</sup> FDCA § 505.

<sup>54</sup> Generally, under the FDCA all “new chemical entity” (NCE) drugs were restricted by the FDA to prescription status and “new drug” requirements encompassed non-prescription drugs that had been converted from prescription status through a supplemental NDA protocol. FDCA § 505(b).

<sup>55</sup> FDCA § 520(f).

<sup>56</sup> FDCA § 502.

<sup>57</sup> FDCA § 301(b).

<sup>58</sup> FDCA § 502(i)(1).

<sup>59</sup> FDCA § 502(f).

which a layperson can understand the use of a drug and its intended purpose.<sup>60</sup> Drug labels must contain: 1) statements of all conditions, purposes, or uses for which such drug is intended, including warnings when the use, method or recommended dosage becomes unsafe, or when duration of administration or application may be dangerous to health; 2) general dose quantities for the drug's intended use by persons of different ages and physical conditions; 3) frequency, duration, time, and route of administration or application of the drug; and 4) any preparations for use that require shaking, dilution, adjustment of temperature, or other manipulation or processes.<sup>61</sup>

The FDCA also prohibits the transportation of adulterated drugs in interstate commerce.<sup>62</sup> Section 501 explains that "adulteration" occurs when a drug becomes impure or unfit for human consumption due to an alteration in composition or formulation.<sup>63</sup> The FDCA deems a drug adulterated if: 1) it consists in whole or in part of any filthy, putrid, or decomposed substance whereby it may have been rendered injurious to health; 2) it purports to be or is represented as a drug name which is recognized in an official compendium (USP or NF), and its strength differs from, or its quality or purity falls below the standard set forth in such compendium; and 3) it has been mixed or re-packaged to reduce its quality or strength, or substituted wholly or in part.<sup>64</sup>

The FDCA also deems a drug adulterated if it is manufactured, prepared, processed, packed, or stored in a facility under unsanitary conditions, or does not conform to the FDA's Current Good Manufacturing Practices (cGMPs).<sup>65</sup> The FDA's cGMPs set standards for the design, monitoring, and control of manufacturing processes in order to ensure the identity, strength, quality, and purity of the drug.<sup>66</sup> cGMPs cover all aspects of the drug manufacturing process including ventilation, air filtration and cooling, equipment maintenance, construction and design, production and processing controls, and the required records and reports by the pharmaceutical manufacturing entity for the facility.<sup>67</sup>

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<sup>60</sup> 21 C.F.R. § 201.5 (2017).

<sup>61</sup> *Id.*

<sup>62</sup> FDCA § 301(a).

<sup>63</sup> FDCA § 501.

<sup>64</sup> FDCA § 501(a)-(d).

<sup>65</sup> FDCA § 501(h).

<sup>66</sup> FDCA § 520(f)(1)(A).

<sup>67</sup> *See Facts About Current Good Manufacturing Practices (cGMPs)*, U.S. FOOD AND

Section 301 of the FDCA provides the FDA authority over compounded drugs under certain circumstances. For instance, the Act prohibits introducing or delivering into interstate commerce: 1) a “new drug” without prior FDA approval;<sup>68</sup> 2) an “adulterated” drug;<sup>69</sup> or 3) a “misbranded” drug.<sup>70</sup> It also prohibits the manufacturing of any adulterated or misbranded drug.<sup>71</sup> Section 302 of the Act also authorizes the United States to seek injunctive relief in federal court to restrain any violations of Section 301,<sup>72</sup> subjects those who have violated the FDCA’s prohibitions to civil fines and criminal penalties,<sup>73</sup> and allows the federal government to seize mislabeled or adulterated drugs or drug products.<sup>74</sup>

Consequently, the FDA can take action over pharmaceutical compounders if the compounders introduce new drugs, misbrand drugs, or sell adulterated drugs in interstate commerce.<sup>75</sup> Initially, the FDA did not use these provisions to regulate compounding,<sup>76</sup> and deferred to the states for the regulation of drug compounding.<sup>77</sup> Also, the FDA did not require compounding pharmacists to file an NDA seeking “new drug” approval for compounded drugs.<sup>78</sup> The FDA has traditionally considered it important to allow pharmacies to provide medication tailored to the needs of individual patients.<sup>79</sup> The FDA also believed that it was impracticable for pharmacies to complete and obtain NDA approval for each compounded drug prepared for each patient-specific medication.<sup>80</sup>

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DRUG ADMIN. (Jan. 6, 2015), <http://www.fda.gov/drugs/developmentapprovalprocess/manufacturing/ucm169105.htm>. For additional guidance on the cGMP process, see FOOD AND DRUG LAW INSTITUTE, HOW TO COMPLY WITH CGMPs (2013); see also 21 C.F.R. §§ 211.46, 211.63-72, 211.100-113, 211.180-198 (2017).

<sup>68</sup> FDCA § 301; see CRS REPORT R43038, *supra* note 44, at 4; FDCA § 505 (new drugs).

<sup>69</sup> FDCA § 301; see CRS REPORT R43038, *supra* note 44, at 4; FDCA § 501(a)(2)(B) (adulteration).

<sup>70</sup> FDCA § 301; see CRS REPORT R43038, *supra* note 44, at 5; FDCA § 502(f)(1) (misbranding).

<sup>71</sup> FDCA § 301; see CRS REPORT R43038, *supra* note 44, at 4.

<sup>72</sup> FDCA § 302(a); see CRS REPORT R43038, *supra* note 44, at 4.

<sup>73</sup> FDCA § 301; see CRS REPORT R43038, *supra* note 44, at 4.

<sup>74</sup> FDCA § 304; see CRS REPORT R43038, *supra* note 44.

<sup>75</sup> See *Med. Ctr. Pharmacy v. Mukasey*, 536 F.3d 383, 395 (5th Cir. 2008) (noting the language of the FDCA’s new drug definition to be “both plain and expansive”); *United States v. Franck’s Lab, Inc.*, 816 F. Supp. 2d 1209, 1237 (M.D. Fla. 2011) (noting that the FDCA’s provision, if “read literally,” would apply to bulk compounding); see CRS REPORT R43038, *supra* note 44, at 4.

<sup>76</sup> *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 362 (2002).

<sup>77</sup> *Id.* at 361.

<sup>78</sup> *Mukasey*, 536 F.3d at 389.

<sup>79</sup> *Thompson*, 535 U.S. at 362.

<sup>80</sup> GAO REPORT, *supra* note 12, at 7. In fiscal year 2013, user fees for NDAs ranged from

Nevertheless, the FDA considers compounded drugs to be “new drugs” that are subject to FDA oversight to ensure that they are safe, effective and made in accordance with federal quality standards.<sup>81</sup> However, because the FDA has limited resources to verify manufacturing quality prior to marketing, compounded drugs could potentially pose health risks should they be sub- or super-potent, contaminated, or otherwise adulterated.

For decades following the passage of the FDCA, regulation of drug compounding was generally left to the states because it was widely recognized that compounded drugs could not meet the FDCA’s drug approval requirements since compounded drugs were traditionally made in small amounts for an individual patient.<sup>82</sup> Also, safety and efficacy trials were impracticable, since compounding pharmacies could not afford testing of the “new drugs” under the NDA approval process for each individual compounded drug.<sup>83</sup>

In the late 1980s and early 1990s, the FDA became aware that some compounding pharmacies were engaging in activities that might have extended beyond “traditional” compounding; for example, by making drugs for interstate sale without a prescription for an individually identified patient.<sup>84</sup> In other instances, these pharmacies were competing with branded products by manufacturing and distributing interstate the generic versions of the branded drugs, which the FDA considers as unapproved “new drugs” in the absence of a completed abbreviated new drug application (ANDA).<sup>85</sup> In other instances, pharmacies were pro-

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\$979,400 to \$1,958,800, depending on whether or not the application required clinical data, and were \$51,520 for ANDAs. See *Federal and State Role in Pharmacy Compounding and Reconstitution: Exploring the Right Mix to Protect Patients: Hearing Before the S. Comm. on Health, Educ., Labor and Pensions*, 108<sup>th</sup> Cong. 38 (2003) (statement of Steven K. Galson, Acting Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration), <https://www.gpo.gov/fdsys/pkg/CHRG-108shrg90129/html/CHRG-108shrg90129.htm> [hereinafter Statement of Steven K. Galson]. According to *Thompson*, 535 U.S. at 369,

[I]t would not make sense to require compounded drugs created to meet the unique needs of patients to undergo the testing required for the new drug approval process. Pharmacists do not make enough money from small-scale compounding to make safety and efficacy testing of their compounded drugs economically feasible, so requiring such testing would force pharmacists to stop providing compounded drugs.

<sup>81</sup> GAO REPORT, *supra* note 12, at 7.

<sup>82</sup> *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 362 (2002).

<sup>83</sup> Statement of Steven K. Galson, *supra* note 80.

<sup>84</sup> Pontikes, *supra* note 1.

<sup>85</sup> *Thompson*, 535 U.S. at 362 (“FDA eventually became concerned, however, that some pharmacists were manufacturing and selling drugs under the guise of compounding, thereby

moting compounded drugs directly to practitioners and patients, receiving and processing large quantities of bulk substances, and compounding drugs without patient-specific prescriptions.<sup>86</sup> The authority of the FDA to regulate compounded drugs did not become an issue until the early 1990s when the FDA became concerned that some pharmacists were engaged in large-scale bulk compounding that was, in the FDA's view, more akin to drug manufacturing and an attempt to circumvent the FDCA's new drug requirements.<sup>87</sup>

There have been notable incidents of compounding pharmacies not producing drugs safely.<sup>88</sup> In response, the FDA published an Alert Letter and warned of enforcement action because some pharmacies were using incorrect procedures and controls when compounding sterile products.<sup>89</sup> The FDA emphasized that pharmacists who prepared batches of sterile drug products were responsible for conforming to current cGMP guidelines, and for using safe packaging to ensure continued sterility during use and warned pharmacists to balance the need to prepare batches of sterile products with their capacity for production.<sup>90</sup>

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avoiding the FDCA's new drug requirements."); *Med. Ctr. Pharmacy v. Mukasey*, 536 F.3d 383, 389-90 (5th Cir. 2008) ("Although [FDA] had long refrained from regulation compounding, it believed that pharmacies engaging in large-scale bulk compounding were . . . using the FDA's traditional lenience toward compounding as an end-run around the new drug approval, adulteration, and misbranding provisions of the FDCA.").

<sup>86</sup> U.S. FOOD & DRUG ADMIN., COMPLIANCE POLICY GUIDE 460.200, PHARMACY COMPOUNDING (1992) (rescinded upon the enactment of the Food and Drug Administration Modernization Act of 1997) [hereinafter CPG 1992].

<sup>87</sup> *Mukasey*, 536 F.3d at 389. The FDA's concern over the practice of compounding has also been, in large part, due to certain patient injuries caused by compounded drugs. See *The Special Risks of Pharmacy Compounding*, U.S. FOOD AND DRUG ADMIN. (Jan. 11, 2017), <https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm107836.htm>. The Agency has asserted that it knows of more than 200 adverse events involving seventy-one compounded products since 1990, including certain instances with "devastating repercussions." *Id.*

<sup>88</sup> For example, in 1989, a pharmacist in Pittsburgh, Pennsylvania prepared indomethacin eye drops that caused severe eye infections in twelve patients – two female patients required removal of one eye. RICHARD R. ABOOD, *PHARMACY PRACTICE AND THE LAW* 134 (Jones and Bartlett Publishers, 6th ed. 2011). Indomethacin was an anti-inflammatory drug produced by the pharmaceutical manufacturer Merck, Sharp & Dohme. *Eye Drop Injuries Prompt an FDA Warning*, N.Y. TIMES, Dec. 9, 1990, at 39. Indomethacin was FDA-approved for pain relief and sold in capsule form. *Id.* The health investigators later determined that pseudomonas bacteria had contaminated an unknown number of the eye drop bottles. *Id.* While indomethacin had not been approved by the FDA for use in eye drop format, such use was not considered illegal. *Id.* Merck defended that it was not responsible for its drug since it had been altered from its FDA-approved capsule form. *Id.* Also in 1989, a hospital pharmacy in Lincoln, Nebraska, prepared surgical solutions that became microbially contaminated, resulting in patient deaths. *Id.*

<sup>89</sup> Marlene Z. Bloom, *Compounding in Today's Practice: Concern About Pharmacists' Right to Compound Has Heated Up Since Compounding Problems Occurred in Pittsburgh, Prompting Increased Interest by FDA*, AM. PHARMACY, Oct. 1991, at 31-32.

<sup>90</sup> *Id.*

The FDA also reviewed its authority to regulate drug compounding and published Compliance Policy Guide 7132.16 (CPG 1992), which attempted to clarify the distinction between drug compounding and drug manufacturing.<sup>91</sup> The CPG 1992 emphasized that the FDA had no intention of regulating pharmacy's historic exemption on compounded drugs pursuant to a valid prescription. CPG 1992 also stated that pharmacists can engage in "anticipatory compounding" and produce limited quantities of drug when they "provide[d] a documented history of receiving valid prescriptions within an established professional relationship between the pharmacy, the practitioner and the patient."<sup>92</sup> Still, the FDA declared that it would initiate enforcement actions when pharmacists went beyond "traditional" compounding and engaged in manufacturing, which would violate the FDCA's "new drug," "adulteration," or "misbranding" provisions.<sup>93</sup>

*B. The FDA Modernization Act § 503A Regulates Compounding, But Ninth Circuit Strikes It Down Because It Includes Unconstitutional Advertising Restrictions*

In order to clarify the FDA's role regarding pharmacy compounding, as part of the Food and Drug Administration Modernization Act (FDAMA) of 1997, Congress added Section 503A<sup>94</sup> to the FDCA.<sup>95</sup>

Section 503A distinguished manufacturing from compounding. It placed restrictions on the use of bulk substances in the compounding process,<sup>96</sup> and prohibited the compounding of copies of branded drugs.<sup>97</sup> Section 503A codified parts of the FDA's CPG 1992<sup>98</sup> and exempted

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<sup>91</sup> CPG 1992, *supra* note 86.

<sup>92</sup> CPG 1992, *supra* note 86.

<sup>93</sup> CPG 1992, *supra* note 86.

<sup>94</sup> Food and Drug Admin. Modernization Act (FDAMA) of 1997, Pub. L. No. 105-115, §127, 111 Stat. 2296 (1997) (codified as amended at 21 U.S.C. § 353 (1997)).

<sup>95</sup> The FDAMA streamlined regulatory procedures to ensure the expedited availability of safe and effective drugs and devices to the public. *Id.* at § 503A. Informally known as the Modernization Act, the objective of the FDAMA was greater patient access to drugs and medical devices by accelerating review of significant new and novel medical products. *Id.*

<sup>96</sup> In November 1998, the FDA issued a Draft Guidance on the enforcement of Section 503A. U.S. FOOD AND DRUG ADMIN., GUIDANCE FOR INDUSTRY: ENFORCEMENT POLICY DURING IMPLEMENTATION OF SECTION 503A OF THE FDCA (1998) [hereinafter 1998 DRAFT GUIDANCE]. The 1998 Draft Guidance primarily focused on Section 503A's limitations on compounding specific drugs including the bulk substances that could be used in compounding, and specific drugs that could not be compounded. *Id.*

<sup>97</sup> FDAMA § 503A.

<sup>98</sup> U.S. FED. FOOD AND DRUG ADMIN., *Guidance for FDA Staff and Industry, Compliance*

drug products compounded by a pharmacist from the FDA's NDA approval process, the requirements that the drug is manufactured in conformity with cGMP, and that the drug's labeling carry adequate directions for use.<sup>99</sup> However, to qualify for these exemptions, the compounding pharmacies had to refrain from advertising, promoting, or soliciting prescriptions.<sup>100</sup> The restrictions on advertising aimed to clamp down on compounding pharmacies promoting their services in a manner that would allow them to be manufacturers and supply drugs nationally.

Government restrictions on advertising are subject to court review to ensure they do not run afoul of the First Amendment guarantee of free speech. In *Central Hudson Gas v. Public Service Commission*, the Supreme Court held that for a regulation to be upheld, the government has the burden of showing that: 1) the government had a substantial interest in the regulation; 2) the regulation directly advanced the government interest; and 3) the burden on speech imposed by the regulation was not more extensive than is necessary to serve the government's interest.<sup>101</sup>

In 1998, in *Western States Medical Center et al. v. Shalala (Western States)*,<sup>102</sup> seven pharmacies sued the FDA, challenging section 503A's restrictions on advertising, promotion, and solicitation, alleging that these restrictions represented an unconstitutional restriction on speech.<sup>103</sup> The U.S. District Court for the District of Nevada struck down section 503A's advertising restrictions.<sup>104</sup> In 2001, the Ninth Circuit Court of Appeals affirmed the holding but also held that these provisions were not severable from the rest of the section and therefore struck down section 503A in its entirety.<sup>105</sup> In 2002, in *Thompson v. Western States Medical Center*, the Supreme Court affirmed the lower court rulings, but because neither party petitioned for certiorari on the severability issue, the Court did not review that portion of the Court of Appeals' decision.<sup>106</sup>

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*Policy Guides Manual, Sec. 460.200, Pharmacy Compounding (May 2002) [hereinafter CPG 2002].*

<sup>99</sup> *Id.*

<sup>100</sup> FDAMA § 503A(c).

<sup>101</sup> *Central Hudson Gas v. Public Service Commission*, 447 U.S. 557, 564 (1980).

<sup>102</sup> *W. States Med. Ctr. v. Shalala*, 69 F. Supp. 2d 1288, 1292 (D. Nev. 1999).

<sup>103</sup> *Id.*

<sup>104</sup> *Id.*

<sup>105</sup> *W. States Med. Ctr. v. Shalala*, 238 F.3d 1090 (9th Cir. 2001), *aff'd sub nom.* *Thompson v. W. States Med. Ctr.*, 535 U.S. 357 (2002).

<sup>106</sup> *Thompson v. W. States Med. Ctr.*, 535 U.S. at 360 (2002).

Because of the confusion regarding the extent of the FDA's authority to regulate compounding after this decision, the agency decided to issue guidance regarding the factors it would consider when determining whether to take enforcement action against compounding pharmacies for FDCA violations.<sup>107</sup> The FDA issued a Compliance Policy Guide in 2002 (CPG 2002), which was similar to its earlier compliance guide issued in 1992 (CPG 1992).<sup>108</sup> CPG 2002 distinguished between traditional compounding and what the FDA viewed as "manufacturing and distributing" under the guise of pharmacy compounding.<sup>109</sup> The guidance noted that the agency would continue to defer to state pharmacy authorities for "less significant" violations of the FDCA that were related to pharmacy compounding of human drugs.<sup>110</sup> However, the agency would initiate enforcement action when a compounding pharmacy's activity resembled those of a drug manufacturer which results in violations of the "new drug," "adulteration," or "misbranding" provisions of the FDCA.<sup>111</sup>

The CPG 2002 listed nine circumstances under which the FDA was likely to bring enforcement actions. These included: 1) compounding of drugs in anticipation of receiving prescriptions, except in very limited quantities; 2) compounding drugs that were removed from the market due to safety reasons; 3) compounding finished drugs from bulk active ingredients that are not components of approved FDA drugs without an IND application; 4) receiving, storing, or using drug substances without obtaining written assurance from the supplier that each drug substance lot has been processed at FDA registered facilities; 5) receiving, storing, or using drug components that are not guaranteed or otherwise determined to meet official compendia requirements; 6) using commercial-scale manufacturing or testing equipment for drug compounding products; 7) compounding drugs for third parties who resell to individual patients or offering compounded drug products at wholesale to other state-licensed persons or commercial entities for resale; 8) compounding drug

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<sup>107</sup> CPG 2002, *supra* note 98, at 1; FDAMA § 127.

<sup>108</sup> CPG 2002, *supra* note 98.

<sup>109</sup> For example, the FDA specifically identified the firms receiving and using large quantities of bulk drug substances to manufacture large quantities of unapproved drug products in advance of a valid prescription may be "far more consistent with drug manufacturers and wholesalers than with those of retail pharmacies." CPG 2002, *supra* note 98, at 3. The restrictions are included in 21 U.S.C. § 353a(c).

<sup>110</sup> CPG 2002, *supra* note 98.

<sup>111</sup> CPG 2002, *supra* note 98.

products that are commercially available in the marketplace or that are essentially copies of commercially available FDA-approved drug products;<sup>112</sup> and 9) failing to operate in conformance with applicable state law.<sup>113</sup>

*C. The Fifth Circuit Upholds § 503A except its Advertising Restrictions*

In 2004, in *Medical Center Pharmacy v. Mukasey (Medical Center Pharmacy)*,<sup>114</sup> ten pharmacies challenged the FDA's authority to regulate compounded drugs, particularly the CPG 2002 guidelines.<sup>115</sup> The pharmacies asked the court to declare that: 1) compounded drugs are not subject to the FDCA "new drug" requirement; 2) the FDCA permits pharmacists to compound drugs from bulk ingredients for non-food producing animals; and 3) pharmacies that comply with certain provisions of the FDCA are exempt from the Act's records inspection provisions.<sup>116</sup>

The U.S. District Court for the Western District of Texas ruled in favor of the plaintiffs, holding that compounded drugs when created for an individual patient pursuant to a prescription from a licensed practitioner "are implicitly exempt" from the FDCA's "new drug" approval process.<sup>117</sup> The court also declared that in light of *Western States*, the remainder of section 503A was severable.

The Fifth Circuit Court of Appeals, however, overturned the District Court and held that compounded drugs are subject to the new drug approval, adulteration, and misbranding requirements.<sup>118</sup> The court reasoned that Congress would not have enacted the FDAMA's provisions

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<sup>112</sup> In certain circumstances, it may be appropriate for a pharmacist to compound a small quantity of a drug that is only slightly different than an FDA approved drug that is commercially available. CPG 2002, *supra* note 98. In these circumstances, the FDA will consider whether there is documentation of the medical need for the particular variation of the compounded drug for the particular patient. *Id.*

<sup>113</sup> CPG 2002, *supra* note 98, at 4.

<sup>114</sup> *Med. Ctr. Pharmacy v. Mukasey*, 536 F.3d 383 (5th Cir. 2008).

<sup>115</sup> *Id.* at 391.

<sup>116</sup> *Id.* at 392; Pontikes, *supra* note 1.

<sup>117</sup> *Med. Ctr. Pharmacy v. Gonzales*, 451 F. Supp. 2d 854, 858 (W.D. Tex. 2006), *vacated in part sub nom. Med. Ctr. Pharmacy v. Mukasey*, 536 F.3d 383 (5th Cir. 2008).

<sup>118</sup> *Med. Ctr. Pharmacy v. Mukasey*, 536 F.3d 383, 409 (5th Cir. 2008). The Fifth Circuit vacated the district court's judgment and remanded the case to the district court for further proceedings. *Id.*; see GAO REPORT, *supra* note 12, at 35.

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exempting compounded drugs from the FDCA's "new drug" requirements had these provisions not applied to compounded drugs.<sup>119</sup> The court also found, contrary to the Ninth Circuit, that the severability clause applied to section 503A.<sup>120</sup> The court explained that if Congress did not want the FDCA's severability clause to apply to section 503A, it would have specifically said so and that there was no strong evidence that Congress would not have enacted section 503A without the advertising provisions.<sup>121</sup>

As a result, in the Fifth Circuit, compounded drugs represented "new drugs" under the FDCA but were expressly exempt from the "new drug" requirements if the drug sponsor complied with section 503A, notwithstanding the provisions restricting advertising that the court held to be unconstitutional.<sup>122</sup> The parties in *Medical Center Pharmacy* did not petition the Supreme Court for review; thus, uncertainty remains regarding the FDA's authority to regulate compounded drugs as "new drugs."

#### D. FDA Oversight After the Circuit Split

The *Western States* and *Medical Center Pharmacy* judicial decisions directly conflict regarding whether the non-speech provisions of section 503A are severable and remain in effect. As a result of the Fifth and Ninth Circuit split, the FDA developed distinct enforcement policies for different circuits.

The *Western States* decision invalidated all of section 503A, so the regulatory standards for quality, including those for compounding pharmacies, had no effect in the Ninth Circuit states (i.e., Alaska, Arizona, California, Hawaii, Idaho, Montana, Nevada, Oregon, and Washington).<sup>123</sup> In those states, the FDA adopted the approach that all compounded drugs were "new drugs" under the FDCA, and determined that

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<sup>119</sup> *Mukasey*, 536 F.3d at 400 ("In 1997, Congress enacted the FDAMA as an amendment to the FDCA. That amendment provides considerable evidence that Congress sought to address pharmacy compounding directly and that it did so with the assumption that the 'new drug' provision applies to drugs created through pharmacy compounding."); see also GAO REPORT, *supra* note 12, at 35.

<sup>120</sup> *Mukasey*, 536 F.3d at 401-02, 404-05 ("[W]e conclude that the invalidated portion of FDAMA is severable and that its surviving portions therefore remain in effect."); see GAO REPORT, *supra* note 12, at 35.

<sup>121</sup> *Mukasey*, 536 F.3d at 401-02, 404-05; see GAO REPORT, *supra* note 12, at 35.

<sup>122</sup> *Mukasey*, 536 F.3d at 405; see GAO REPORT, *supra* note 12, at 35.

<sup>123</sup> The Ninth Circuit Court of Appeals decision also applies to the FDA's authority over certain compounding pharmacies located in Colorado, New Jersey, Tennessee, Texas, and Wisconsin, as these pharmacies were party to the lawsuit. *Thompson v. W. States Med. Ctr.*, 535 U.S.

whether to take enforcement action against a compounding pharmacy would be based on whether the pharmacy had engaged in any of the activities outlined in the CPG 2002.<sup>124</sup> In any event, its compounded drug was still subject to all of the FDCA requirements for new drugs. The FDA continued to subject compounding pharmacies to the policies articulated in CPG 2002 for compounding pharmacies in the rest of the country, except in the Fifth Circuit.<sup>125</sup>

In contrast, the *Medical Center Pharmacy* decision upheld all of section 503A, except the advertising, promotion, and solicitation restrictions, and so the regulatory standards for quality, including those for compounding pharmacies, had the force of law in the Fifth Circuit states (i.e., Louisiana, Mississippi, and Texas).<sup>126</sup> In those states, the FDA determined whether a compounded drug met the section 503A exemption from certain FDCA requirements that would preclude the agency from taking enforcement action against a drug compounder.

However, the FDA continued to assert regulatory authority over compounding pharmacies based on its “enforcement discretion” to regulate “new drugs.” In circumstances where the FDA believed that a pharmacy met the requirement of section 503A, it required strict compliance with cGMP regulations. For example, in a Warning Letter issued in 2001 to Professional Compounding Centers of America, the FDA found significant violations of cGMP regulations, including inadequate air-handling processes, and defective drug-testing and cleaning processes, resulting in a high risk potential for drug contamination.<sup>127</sup>

The FDA subsequently discovered numerous other pharmacies in violation of cGMPs, and concluded that noncompliant pharmacies raised public health risks and dangers to human life.<sup>128</sup> The FDA also ex-

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357, 360 (2002).

<sup>124</sup> *Id.* at 370.

<sup>125</sup> *Id.* Interestingly, however, the FDA did not issue any Warning Letters to compounding pharmacies in Texas, Louisiana or Mississippi applying section 503A. Warning Letter from U.S. Food and Drug Admin. to J & F Int’l. Inc. (Apr. 9, 2010), <https://web.archive.org/web/20110522122632/http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2010/ucm208772.htm>. Outside of the Fifth Circuit, FDA proceeded under its post-*Western States* policy. *Id.*

<sup>126</sup> Warning Letter from U.S. Food and Drug Admin. to Steven’s Pharmacy (Nov. 12, 2008), <https://web.archive.org/web/20090709190819/http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2008/ucm1048074.htm>; Pontikes, *supra* note 1.

<sup>127</sup> Warning Letter from U.S. Food and Drug Admin. to Prof’l Compounding Ctr’s. of America, Inc. (Jul. 27, 2001), <http://casewatch.org/fdawarning/comp/pcca.shtml>; Pontikes, *supra* note 1.

<sup>128</sup> Pontikes, *supra* note 1.

pressed concerns over public health risks associated with the compounding and distribution of drugs that had been withdrawn or removed from the market for safety or efficacy related reasons.<sup>129</sup> To qualify for the compounding exemption of section 503A, one of the conditions was to refrain from compounding drugs that were either withdrawn or removed from the market due to safety or efficacy reasons.

For instance, in 2001, the FDA issued a Warning Letter to Custom Care Pharmacy, which compounded strontium chloride SR-89, the active pharmaceutical ingredient found in the FDA-approved and commercially available drug Metastron.<sup>130</sup> The FDA considered this activity to lie outside “traditional” pharmacy compounding because Custom Care Pharmacy lacked documentation and data substantiating efficacy claims that the compounded product acted differently from the commercially available Metastron.<sup>131</sup>

Also in 2001, the FDA sent a Warning Letter to Unique Pharmaceuticals, a pharmacy that compounded injectable sterile drug products with equivalent dosage and strength similar to the commercially available product.<sup>132</sup> The FDA expressed concerns of Unique Pharmaceuticals’ business structure regarding the quantities of compounded products that it sold to wholesalers. For example, during a three-month period, Unique Pharmaceuticals prepared and distributed 38,650 vials of dexamethasone and 38,400 vials of triamcinolone acetonide.<sup>133</sup> Unique Pharmaceuticals did not prepare compounded drugs for identified, individual patients based on prescription orders, but rather distributed the compounded drugs to wholesalers for further sale to hospitals, pharmacies, and physicians.<sup>134</sup> According to the FDA, Unique Pharmaceuticals op-

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<sup>129</sup> Pontikes, *supra* note 1.

<sup>130</sup> Warning Letter from U.S. Food and Drug Admin. to Custom Care Pharmacy (Oct. 3, 2001), <https://web.archive.org/web/20111008013049/http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2001/ucm178290.htm>; *see* Pontikes, *supra* note 1.

<sup>131</sup> Pontikes, *supra* note 1.

<sup>132</sup> Warning Letter from U.S. Food and Drug Admin. to Unique Pharmaceuticals, Ltd. (Oct. 10, 2001), <https://web.archive.org/web/20090827094727/http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2001/ucm178396.htm> [hereinafter Unique Pharmaceuticals Warning Letter]; *see* Pontikes, *supra* note 1.

<sup>133</sup> Pontikes, *supra* note 1, at n.80; Unique Pharmaceuticals Warning Letter, *supra* note 132 (“Of the 10 products identified by [the] FDA in the Warning Letter, only one of the products had a lower volume, with less than a thousand vials over a three-month period (650 vials of dicyclomine).”).

<sup>134</sup> Unique Pharmaceuticals Warning Letter, *supra* note 132. According to Pontikes, The same pharmacy also had received a Warning Letter from the Texas Department of

erated more like a manufacturer and distributor than a “traditional” compounding pharmacy.<sup>135</sup>

To assess the qualification for a section 503A exemption for a compounding pharmacy, the FDA determined whether the pharmacy offered to sell drug products without a prescription, and whether the API was a component of an FDA-approved drug or was listed in an approved monograph in the USP or the NF. In 2002, the FDA initiated several enforcement actions when it found APIs that were ineligible for use in compounding. The FDA sent Warning Letters to three pharmacies that promoted nicotine lollipops and nicotine lip balm for smoking cessation and for reduction of nicotine addiction.<sup>136</sup> According to the FDA, the nicotine products were considered “new drugs” and did not qualify for the section 503A compounding exemption because they were sold without valid patient-specific prescriptions.<sup>137</sup> Additionally, the API nicotine salicylate was neither a component of an FDA-approved drug nor listed in a USP or NF monograph, and therefore was not a qualified bulk drug substance designated for compounding.<sup>138</sup>

#### IV. *Obstacles to FDA Oversight and Calls for Greater FDA Regulation of Drug Compounding*

Prior to the NECC crisis, several factors limited FDA oversight of

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Health on September 29, 2000, more than a year before the FDA’s October 10, 2001 Warning Letter. [The] FDA, Texas Department of Health, and Texas State Board of Pharmacy had conducted an inspection on August 2, 4, and 16, and [on] September 5, 2000. While the Texas Department of Health issued its Warning Letter about three weeks after the inspection, it took the FDA more than a year to prepare and send its Warning Letter, consistent with the findings of the Texas Department of Health.

Pontikes, *supra* note 1, at n.82.

<sup>135</sup> Pontikes, *supra* note 1, at n.79 (citing Unique Pharmaceuticals Warning Letter, *supra* note 132) (“For example, the FDA identified 10 compounded products that were made in the same dosage strengths as commercially available products that were sold to wholesale drug distributors for subsequent distribution to hospitals, pharmacies and physicians.”). The FDA acknowledged that some of the products may have been in short supply and not commercially available for a brief period of time. *Id.* However, in the FDA’s estimation, the large quantities of drugs prepared and distributed exceeded the limited quantities that may have been needed to meet demand during the temporary shortages. *Id.*

<sup>136</sup> Warning Letter from U.S. Food and Drug Admin. to Ashland Drug (Apr. 9, 2002), <https://web.archive.org/web/20090710114912/http://www.fda.gov/downloads/Drugs/Guidance-ComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeof-ViolationLetterstoPharmaceuticalCompanies/UCM164561.pdf>; Pontikes, *supra* note 1.

<sup>137</sup> Pontikes, *supra* note 1.

<sup>138</sup> Pontikes, *supra* note 1, at n.86 (“While nicotine and nicotine polacrilex were components of FDA-approved drugs that did not qualify for the different salt form, the nicotine salicylate used in the lollipops and lip balm [were] for use in compounding.”).

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compounding pharmacies. The FDA has limited statutory authority. At the same time, some firms affected by compounding pharmacies requested that the FDA regulate compounding pharmacies, while compounding pharmacies resisted FDA oversight. As a result, the FDA was caught in the middle and subject to pressure to move in different directions.

*A. Limited FDA Inspection Authority*

The Fourth Amendment of the Constitution protects individuals from unreasonable search and seizures. Search warrants are issued to authorized law enforcement officers only after a court has found that there is probable cause.<sup>139</sup> Similarly, FDA inspections must comply with the Fourth Amendment requirements, as well as the FDCA requirements regarding inspections. Specifically, section 704 of the FDCA states that FDA inspectors may inspect facilities where drugs are held at reasonable times, within reasonable limits and a reasonable manner. It exempts from FDA inspections pharmacies that regularly dispense prescriptions, and do not manufacture, prepare, or compound drugs for sale other than in the regular course of the retail business.<sup>140</sup>

Legal challenges to the FDA's authority to inspect compounding pharmacies undermine the agency's ability to identify problems and to take appropriate enforcement actions. Suspect entities often refuse to grant the FDA access to facilities and records unless the FDA has a warrant, citing the FDCA's provision which limits the agency's inspection authority over a pharmacy operating in compliance with state and local laws and with the Fourth Amendment.<sup>141</sup>

For example, in *Wedgewood Village Pharmacy, Inc. v. United States*, 421 F.3d 263, 265 (2005), concerned that the pharmacy was producing large quantities of drugs, the FDA obtained a search warrant to inspect the facility. The plaintiff challenged the FDA's authority to inspect the pharmacy for compounding violations, and filed a motion to

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<sup>139</sup> U.S. Const. amend. IV. states:

The right of the people to be secure in their persons, houses, papers, and effects, against unreasonable searches and seizures, shall not be violated, and no warrants shall issue, but upon probable cause, supported by oath or affirmation, and particularly describing the place to be searched, and the persons or things to be seized.

<sup>140</sup> Robert M. Spiller, *How to Handle an FDA Inspection*, 33 FOOD DRUG COSM. L.J. 101 (1978); Eve E. Bachrach, *The Food and Drug Administration Cosmetic Inspection: An Industry Approach*, 38 FOOD DRUG COSM. L.J. 373 (1983).

<sup>141</sup> 21 U.S.C. § 372 (2011).

dismiss the warrant on the grounds that pharmacies were exempt from FDA inspection due to the lack of jurisdiction over state-licensed pharmacies.<sup>142</sup> The *Wedgewood* court held that Congress intended the FDA to be granted the authority to inspect pharmacies in order to determine whether the exemption applied.<sup>143</sup> The court also ruled that because the FDA had probable cause to believe that the pharmacy was manufacturing drugs, the FDA had the authority to also inspect the pharmacy records.<sup>144</sup> Nevertheless, FDA inspection authority is still limited by state statutes and the Fourth Amendment.<sup>145</sup>

### B. *The FDA's Limited Access to Relevant Information*

There is no requirement that compounders report adverse events to federal authorities, so the actual number of individuals harmed by compounded drugs is unknown,<sup>146</sup> and state reporting requirements vary.<sup>147</sup> Thus, the FDA often lacks timely and reliable data on compounding pharmacies, such as the types of drugs being compounded and the adverse events related to the use of compounded drugs.<sup>148</sup> Additionally, prior to the NECC crisis, the FDA was not able to collect timely and reliable data on compounded drugs and on the entities that produced

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<sup>142</sup> *Wedgewood Village Pharmacy, Inc. v. United States*, 421 F.3d 263, 266 (2005).

<sup>143</sup> *Id.* at 269.

<sup>144</sup> *Id.* at 275.

<sup>145</sup> *See generally id.*

<sup>146</sup> Generally, if a manufacturer receives drug- or certain device-related adverse event reports, it must send them to the FDA. 21 C.F.R. §§ 314.80(c), 803.30, 803.50. Health care professionals and consumers can voluntarily file adverse event reports with the FDA and may also report these events to the products' manufacturer. *Id.* User facilities (e.g., hospitals and nursing homes) must report certain device-related, but not drug-related-adverse events to the FDA as well. *Id.*; see also GAO REPORT, *supra* note 12, at 16; THAUL, *supra* note 48; AMALIA K. CORBY-EDWARDS, REGULATION OF DIETARY SUPPLEMENTS, CRS REPORT R43062, at 4 (2014); CTR. FOR DRUG EVALUATION AND RESEARCH, GUIDANCE FOR INDUSTRY (1997), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM299138.pdf>; *Questions and Answers on FDA's Adverse Event Reporting System (FAERS)*, U.S. FOOD AND DRUG ADMIN. (May 5, 2016), <http://www.fda.gov/drugs/guidancecompliance/regulatoryinformation/surveillance/adversedrugs/default.htm>.

<sup>147</sup> A few, but not all, states require some form of reporting of adverse incidents from compounded drugs. See *A Legislative History and Summary of Laws*, NAT'L COUNCIL OF STATE LEGISLATORS (Oct. 1, 2014), <http://www.ncsl.org/issues-research/health/regulating-compounding-pharmacies.aspx>; see also Reporting about healthcare-associated infections and serious reportable events, and serious adverse drug events; charges or reimbursement for resulting services prohibiting, 190TH MASS. GEN. LEG. § 51H (Mass. 2015); Texas Food, Drug, And Cosmetic Act, TEX. HEALTH & SAFETY CODE ANN. tit. 6, ch. 431 (2016).

<sup>148</sup> U.S. GOV'T ACCOUNTABILITY OFF., GAO-08-970, DRUG SAFETY: BETTER DATE MANAGEMENT AND MORE INSPECTIONS ARE NEEDED TO STRENGTHEN FDA'S FOREIGN DRUG INSPECTION PROGRAM (2008); see also GAO REPORT, *supra* note 12, at 15.

them, because under the FDCA compounding pharmacies were not required to register with the FDA or list the products that they produced.<sup>149</sup> In contrast, drug manufacturers are required to register with the FDA and provide information such as the company name, location, and the drugs that the company produces.<sup>150</sup> The FDA therefore could not routinely identify and inspect suspect compounding pharmacies.<sup>151</sup> The FDA typically inspected compounding pharmacies only in response to complaints or adverse events.<sup>152</sup> Furthermore, the agency's Field Accomplishments and Compliance Tracking System (FACTS) did not indicate the agency's final determination of an official action, or whether any action had been taken following an inspection, and could not even distinguish between the inspections of human or veterinary drug manufacturers.<sup>153</sup>

Despite not being required to register, a few compounding pharmacies, such as Ameridose, voluntarily registered with the agency as manufacturers and marketed themselves as "FDA Registered" entities, which allowed them to appear as "registered manufacturers" in the FDA's drug registration database and listing system.<sup>154</sup> However, registering as a manufacturer did not give the FDA authority to require the pharmacy to comply with the FDA's cGMP requirements, which is normally applied to drug manufacturers.<sup>155</sup> In addition, some pharmacies that compounded drugs on large scale and marketed themselves as "FDA Registered" have led state officials, healthcare professionals and the public to assume they were in full compliance with FDA regulations.<sup>156</sup> Adding to the problem, states were also likely to mistakenly assume that "FDA Registered" pharmacies were actively regulated by the FDA and not subject to state oversight.<sup>157</sup>

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<sup>149</sup> Pharmacies are not required to register with the FDA if they follow any applicable local laws regulating the practice of pharmacy and medicine, regularly engage in dispensing drugs upon a prescription from a licensed practitioner, and do not manufacture, prepare, or compound drugs for sale other than during the regular course of their business of dispensing or selling drugs at retail. 21 U.S.C. § 360(g)(1); *see also* GAO REPORT, *supra* note 12, at 9.

<sup>150</sup> GAO REPORT, *supra* note 12, at 9.

<sup>151</sup> GAO REPORT, *supra* note 12, at 14.

<sup>152</sup> GAO REPORT, *supra* note 12, at 17.

<sup>153</sup> GAO REPORT, *supra* note 12, at 28.

<sup>154</sup> GAO REPORT, *supra* note 12, at 14.

<sup>155</sup> GAO REPORT, *supra* note 12, at 14.

<sup>156</sup> GAO REPORT, *supra* note 12, at 14.

<sup>157</sup> Memorandum from U.S. Drug and Food Admin. to Comm. staff, Timeline of FDA Interactions with NECC and Ameridose (Feb. 1, 2013) [hereinafter FDA Timeline]; *see also* NECC AND AMERIDOSE, *supra* note 2, at 21; GAO REPORT, *supra* note 12, at 27.

C. *Drug Manufacturers Pressure the FDA to Act Against Compounding Pharmacies*

Some drug manufacturers exerted pressure on the FDA to increase investigations of compounding pharmacies. For instance, in a citizen petition, Wyeth asked the FDA to initiate enforcement actions against pharmacies compounding “bioidentical” hormone replacement therapies.<sup>158</sup> Similarly, KV Pharmaceutical filed suit to force the FDA to initiate enforcement actions against pharmacies compounding hydroxyprogesterone caproate.<sup>159</sup> The FDA has often been pulled in different directions between manufacturers that want the agency to regulate compounding pharmacies more strictly and compounding pharmacies that resist FDA oversight.

1. *Wyeth’s Citizen Petition*

Wyeth’s 2005 citizen petition requested that the FDA initiate enforcement actions under CPG 2002 against pharmacies that were compounding “bioidentical” hormone replacement therapies.<sup>160</sup> Wyeth marketed the branded prescription medications Prempro, Premphase, and Premarin, estrogen-based hormone therapies used for the treatment of post-menopausal symptoms.<sup>161</sup> According to Wyeth, compounding pharmacies were making unsubstantiated claims regarding the safety risks of using their compounded products without providing similar warning labels that Wyeth was required to include under the FDCA.<sup>162</sup> Moreover, some of the compounded hormone therapies that the pharmacies advertised contained the estrogen analogue estriol, which was not a component of any FDA-approved drug.<sup>163</sup>

In response, the pharmacies argued that estriol had been used as a component of compounded hormone replacement therapy for decades and compounding drugs containing estriol met the specific needs of

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<sup>158</sup> Citizen Petition on Behalf of Wyeth, FDA Docket No. 2005-P-0411 (Oct. 6, 2005) [hereinafter Wyeth Citizen Petition].

<sup>159</sup> 17-hydroxyprogesterone caproate is commonly known as 17P. Press Release, U.S Food & Drug Admin., Updated FDA Statement on Compounded Versions of hydroxyprogesterone caproate (June 15, 2012), <https://web.archive.org/web/20120618021301/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm308546.htm>.

<sup>160</sup> Wyeth Citizen Petition, *supra* note 158; Pontikes, *supra* note 1; CPG 2002, *supra* note 98.

<sup>161</sup> Wyeth Citizen Petition, *supra* note 158, at 7.

<sup>162</sup> Wyeth Citizen Petition, *supra* note 158, at 8-11.

<sup>163</sup> Wyeth Citizen Petition, *supra* note 158, at 9.

women needing hormone replacement therapy.<sup>164</sup> They also indicated that estriol was approved by the Boards of Pharmacies of all fifty states, allowed by the Pharmacy Compounding Accreditation Board, and had long been listed in the USP monograph.<sup>165</sup>

In 2008, almost three years after Wyeth filed its citizen petition and after receiving more than 70,000 public comments, the FDA denied Wyeth's citizen petition request that the FDA take enforcement action against these compounding pharmacies, but on the same day, sent Warning Letters based on the CPG 2002 to seven compounding pharmacies regarding preparations containing estriol used for hormone replacement therapy.<sup>166</sup> The agency explained that enforcement was necessary because the API was not a component of an FDA-approved drug and that the compounding pharmacies made unsubstantiated claims that estriol was effective for hormone replacement therapy.<sup>167</sup> In response to the FDA Warning Letters, industry organizations supporting the compounding pharmacies<sup>168</sup> jointly wrote to the FDA to protest the agency's enforcement actions.<sup>169</sup> They argued that the FDA had overextended the authority of the CPG 2002 and insisted that the compliance policy guide was created without an opportunity for public comment.<sup>170</sup>

Due to the split between the Fifth and Ninth Circuit, the FDA enforced different standards depending on the region. Hence, the compounding of estriol was legal for pharmacies in the Fifth Circuit states of Louisiana, Mississippi, and Texas, and based on the CPG 2002, the

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<sup>164</sup> Wyeth Citizen Petition, *supra* note 158, at 9.

<sup>165</sup> J. Goodrum, *Estriol: Women's Choice vs. a Manufacturer's Greed*, 12 INT'L J. PHARM. COMPOUNDING 287 (2008); see Pontikes, *supra* note 1; see also FDA Response to Wyeth Citizen Petition, FDA Docket No. 2005P-0411/CPI & SUP1 (Jan. 9, 2008).

<sup>166</sup> Press Release, U.S. Food and Drug Admin., FDA Takes Action Against Compounded Menopause Therapy Drugs (Jan. 9, 2008); Warning Letter from U.S. Food and Drug Admin. to Pharmacy Compounding Specialties (Jan. 7, 2008).

<sup>167</sup> Pontikes, *supra* note 1. During the press conference held two days after the FDA denied Wyeth's citizen petition, FDA claimed that the actions taken in sending the Warning Letters were not as a result of the Wyeth citizen petition, that the issues raised in the Warning Letters predated Wyeth's petition, and that Wyeth's request of enforcement actions by a citizen petition was not an appropriate process. *Id.* Yet in sending the Warning Letters the same day it responded to the citizen petition, the FDA did exactly what Wyeth was asking it to do. *Id.*

<sup>168</sup> Pontikes, *supra* note 1. The industry organizations included the American Pharmacists Association, the International Academy of Compounding Pharmacists, the National Community Pharmacists Association, the National Alliance of State Pharmacy Associations, and the American College of Apothecaries. *Id.*

<sup>169</sup> Industry Letter to FDA Comm'r von Eschenbach (Nov. 17, 2008), <http://ncpa.co/pdf/letter-compoundingfdacorres20081117.pdf>; Pontikes, *supra* note 1.

<sup>170</sup> Industry Letter to FDA Comm'r von Eschenbach, *supra* note 169.

FDA maintained enforcement actions against pharmacies outside the Fifth Circuit. The Warning Letters the FDA sent to pharmacies regarding hormone replacement compounded drugs highlighted the agency's inconsistent application of policy.

## 2. *KV Pharmaceutical Suit against the FDA*

In 2011, the FDA approved KV Pharmaceutical's NDA for Makena for use in reducing the risk of preterm birth.<sup>171</sup> Makena was granted orphan drug status by the agency, a program that provides numerous development incentives, including seven years of marketing exclusivity and tax credits for qualified clinical research.<sup>172</sup> In 2012, KV Pharmaceutical sought to force the FDA to take action against pharmacies compounding preparations of hydroxyprogesterone caproate, the API in its branded drug Makena. However, hydroxyprogesterone caproate had been previously available since 1956 under the trade name Delalutin, and pharmacies had compounded hydroxyprogesterone caproate for many years for use in gynecological disorders prior to KV Pharmaceutical's launching of Makena.<sup>173</sup> Seeking to enforce its market exclusivity, KV Pharmaceutical also sent letters to pharmacies compounding hydroxyprogesterone caproate advising them that Makena had been FDA-approved, and that the agency would no longer allow pharmacies to compound hydroxyprogesterone caproate.<sup>174</sup>

KV Pharmaceutical also hired a corporate intelligence firm to obtain and test samples of the compounded version for potency and purity, and found that 80 percent of the compounded drug did not meet purity specifications established by cGMP.<sup>175</sup> KV Pharmaceutical alleged that the API hydroxyprogesterone caproate used in the compounded products

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<sup>171</sup> U.S. Food and Drug Admin., NDA No. 021945 (approved Feb. 3, 2011); Pontikes, *supra* note 1.

<sup>172</sup> Patent & Exclusivity Information for Makena, ORANGE BOOK: APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS, <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OfficeofScienceandHealthCoordination/ucm2018190.htm> (search by "proprietary name"). Orphan drug status is granted for "new drugs" used to treat diseases that affects fewer than 200,000 people in the U.S., or affecting greater than 200,000 people with the expectation that the drug manufacturer is unlikely to recover the cost of drug discovery and development. See U.S. Food and Drug Admin., *Office of Orphan Products Development* (Jan. 5, 2017); Pontikes, *supra* note 1.

<sup>173</sup> *K-V Pharm. Co. v. Fed. Food and Drug Admin.*, 889 F. Supp. 2d 119, 124 (D.D.C. 2012).

<sup>174</sup> *Id.* at 125.

<sup>175</sup> Walt Bogdanich & Sabrina Tavernise, *U.S. Concern Over Compounders Predates Outbreak of Meningitis*, N.Y. TIMES, Oct. 22, 2012.

was imported in bulk by Chinese companies that were not registered with the FDA.<sup>176</sup> The FDA had been aware of compounders increasingly buying raw unapproved ingredients from foreign sources. The FDA subsequently conducted tests of both API and finished compounded products, but did not identify any major safety problem with the compounded hydroxyprogesterone caproate products.<sup>177</sup> In 2011, the FDA stated that it did not intend to take enforcement action against pharmacies compounding hydroxyprogesterone caproate for valid prescriptions, unless the compounder violated standards related to safety or efficacy.<sup>178</sup>

Dissatisfied, KV Pharmaceutical sued the FDA seeking an injunction compelling the agency to take action against pharmacies compounding hydroxyprogesterone caproate.<sup>179</sup> The district court dismissed the complaint, holding that the FDA had discretion to initiate enforcement actions and that the courts lacked authority to review such decisions.<sup>180</sup> The courts also held that it could not direct FDA enforcement activities, particularly when the actions involve the FDA's expertise.<sup>181</sup> However, the court did not discuss whether the statute allowed FDA enforcement discretion. Thus, the FDA continued to have the authority to regulate drug manufacturing and focused enforcement on compounding practices that it believed were akin to drug manufacturing.

## V. *The New England Compounding Center Crisis*

### A. *FDA Oversight of NECC*

NECC had been under FDA scrutiny since March 2002, when two adverse events were reported through MedWatch, the FDA's Safety Information and Adverse Event Reporting Program. The FDA defines an adverse event as "any undesirable experience associated with the use of a medical product in a patient" and explains that such an event "should

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<sup>176</sup> *Id.*

<sup>177</sup> Press Release, U.S. Food and Drug Admin., Statement on Compounded Versions of hydroxyprogesterone caproate (Feb. 3, 2011) [hereinafter FDA Statement on Makena]; see Pontikes, *supra* note 1.

<sup>178</sup> *K-V Pharm. Co.*, 889 F. Supp. 2d at 125. The FDA stated that it was taking this position in order to support access to hydroxyprogesterone caproate. Pontikes, *supra* note 1.

<sup>179</sup> *Id.* at 122-23; FDA Statement on Makena, *supra* note 177; Pontikes, *supra* note 1.

<sup>180</sup> *K-V Pharm. Co. v. Fed. Food and Drug Admin.*, 889 F. Supp. 2d 119, 144 (D.D.C. 2012); Pontikes, *supra* note 1.

<sup>181</sup> *K-V Pharm. Co. v. Fed. Food and Drug Admin.*, 889 F. Supp. 2d at 134; see FDA Statement on Makena, *supra* note 177; Pontikes, *supra* note 1.

be reported when the patient outcome is death, life-threatening, hospitalization (initial or prolonged), disability or permanent damage, congenital anomaly or birth defect, or requires intervention to prevent permanent impairment or damage (devices), or any other serious important medical events.<sup>182</sup>

Both adverse events involved patients suffering from meningitis symptoms after receiving betamethasone injections from a lot produced by NECC, which subsequently tested positive for contamination.<sup>183</sup> In response, the FDA and the MDPH inspected NECC and issued a Form 483 report, which noted conditions that may violate federal law.<sup>184</sup> The FDA sent NECC a Warning Letter on April 16, 2002, which focused on two violations: 1) the compounded betamethasone's failure to be sterile, and 2) NECC's failure to account for records related to the suspect lot of betamethasone.<sup>185</sup>

In May 2002, hospital staff informed the FDA that vials of methylprednisolone acetate distributed by NECC were contaminated.<sup>186</sup> Methylprednisolone acetate is a steroid that is frequently injected into the spine to treat pain and swelling. By October 2002, Massachusetts and FDA inspectors had returned to NECC in response to three new MedWatch reports of patients hospitalized with meningitis symptoms following administration of methylprednisolone acetate made by NECC.<sup>187</sup>

Prior to the FDA's issuance of a second Warning Letter to NECC, FDA and MDPH officials met in February 2003 to coordinate a joint response.<sup>188</sup> The meeting confirmed that NECC would be treated as a compounding pharmacy, and that Massachusetts would take the lead on further regulatory actions.<sup>189</sup> However, the FDA warned of potential se-

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<sup>182</sup> NECC AND AMERIDOSE, *supra* note 2, at 8.

<sup>183</sup> NECC AND AMERIDOSE, *supra* note 2, at 7.

<sup>184</sup> NECC AND AMERIDOSE, *supra* note 2, at 7.

<sup>185</sup> NECC AND AMERIDOSE, *supra* note 2, at 7.

<sup>186</sup> U.S. FOOD AND DRUG ADMIN., INSPECTION REPORT OF NEW ENG. COMPOUNDING CENTER (2013); *see also* NECC AND AMERIDOSE, *supra* note 2, at 7.

<sup>187</sup> *Id.*

<sup>188</sup> *See* Memorandum from Kristina Joyce, Consumer Safety Officer, New England Dist. Off., FDA & Mark Lookabaugh, Compliance Officer, New England Dist. Off., FDA, to Central File (Feb. 5, 2003) (referring to a meeting with Massachusetts Board of Pharmacy/Division of Professional Licensure at 239 Causeway Street, Boston, MA 02114 on Feb. 24, 2003) [hereinafter FDA Memorandum]; *see* NECC AND AMERIDOSE, *supra* note 2, at 7.

<sup>189</sup> FDA Memorandum, *supra* 188, at 1; *see* NECC AND AMERIDOSE, *supra* note 2, at 7.

rious harm if NECC's compounding practices were not improved, especially the practice relating to compounding sterile drug products.<sup>190</sup>

Later, the FDA received additional information suggesting that the NECC was operating as a manufacturer, rather than a traditional compounding pharmacy. On February 27, 2004, the FDA received a complaint from a law firm representing a drug company regarding NECC's promotion of trypan blue, an ophthalmic dye product used for capsular staining during cataract surgery that the FDA had not approved, but which was similar to an FDA approved branded medication that the complainant produced.<sup>191</sup> In May 2004, the Massachusetts Board of Registration in Pharmacy (MBRP) forwarded to the FDA a letter that it had received from a hospital pharmacist in Iowa which suggested that NECC manufactured trypan blue.<sup>192</sup> The MBRP also forwarded a complaint from a pharmacist in Wisconsin regarding NECC's promotion of a potent topical anesthetic cream.<sup>193</sup>

The trypan blue complaints prompted the FDA's Center for Drug Regulation and Research (CDER) to inspect NECC on June 2, 2004.<sup>194</sup> The FDA conducted the inspection in accordance with the CPG 2002; because Massachusetts is in the First Circuit, the Ninth Circuit decision in *Western States* was not binding. The investigations sought to determine if NECC's activities raised issues associated with a drug manufacturer rather than a traditional compounding pharmacy.<sup>195</sup>

On December 4, 2006, the FDA sent NECC a Warning Letter listing several practices which indicated that NECC was operating as a manufacturer, and informing NECC's President and co-owner Barry Cadden that failure to promptly correct the violations could result in the FDA seizing its products, seeking injunctions, or taking other regulatory action.<sup>196</sup> The Warning Letter reveals that the FDA was aware that NECC operated outside the scope of a traditional compounding pharmacy.<sup>197</sup>

The Warning Letter stated that NECC was: 1) compounding copies

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<sup>190</sup> FDA Memorandum, *supra* 188, at 1; *see* NECC AND AMERIDOSE, *supra* note 2, at 7.

<sup>191</sup> NECC AND AMERIDOSE, *supra* note 2, at 9; *see also* E-mail from Compliance Officer, New England Dist. Off., FDA, to Kathleen Anderson (Feb. 27, 2004, 10:49 EST).

<sup>192</sup> NECC AND AMERIDOSE, *supra* note 2, at 9.

<sup>193</sup> NECC AND AMERIDOSE, *supra* note 2, at 9.

<sup>194</sup> NECC AND AMERIDOSE, *supra* note 2, at 10.

<sup>195</sup> CPG 2002, *supra* note 98, at 3.

<sup>196</sup> Warning Letter from Gail T. Costello, Dist. Dir., New England Dist. Office, FDA, to Barry J. Cadden, Dir. of Pharmacy, New England Compounding Center (Dec. 4, 2006) [hereinafter FDA Warning Letter]; *see also* NECC AND AMERIDOSE, *supra* note 2, at 10.

<sup>197</sup> NECC AND AMERIDOSE, *supra* note 2, at 10.

of commercially available products that were not components of FDA-approved products; 2) compounding standardized anesthetic drug products, which was outside the scope of traditional pharmacy compounding; 3) repackaging Avastin, a sterile injectable product used to treat macular degeneration; and 4) reportedly informing physicians that they could write a staff member, rather than the patient's name on the prescription.<sup>198</sup>

In January 2007, NECC responded that the Warning Letter was based on an inspection started twenty-eight months earlier and that some assertions were no longer correct.<sup>199</sup> NECC argued that the FDA lacked authority over compounded drugs, that it did not need approved New Drug Applications (NDA) before dispensing compounded drugs, and that it did not introduce unapproved "new drugs" into interstate commerce because its medications were not misbranded.<sup>200</sup> NECC insisted that it did not compound copies of commercially available drugs or process or repackage approved drugs in a manner that would subject it to FDA regulation. NECC claimed that it only dispensed compounded medications upon the receipt of valid patient-specific prescriptions.<sup>201</sup>

On June 25, 2007, the FDA received an adverse event report which indicated that a patient had developed severe endophthalmitis and required emergency eye surgery after being administered Avastin, repackaged by NECC, to treat macular degeneration.<sup>202</sup> In its 2006 Warning Letter to NECC, the FDA had noted that splitting Avastin into multiple preservative-free doses created the potential for microbial contamination and could cause endophthalmitis and significant vision loss.<sup>203</sup>

The FDA continued to receive complaints regarding NECC products. In December 2007, a physician complained to the FDA that vials of betamethasone manufactured by NECC appeared to be discolored, with particles settling at the bottom of the vials.<sup>204</sup> Patients complained

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<sup>198</sup> FDA Warning Letter, *supra* note 196; *see also* NECC AND AMERIDOSE, *supra* note 2, at 10.

<sup>199</sup> NECC AND AMERIDOSE, *supra* note 2, at 12; *see also* Letter from Barry J. Cadden, Dir. of Pharmacy, NECC, to Compliance Officer, New England Dist. Off., FDA at 1 (Jan. 5, 2007).

<sup>200</sup> NECC AND AMERIDOSE, *supra* note 2, at 12.

<sup>201</sup> NECC AND AMERIDOSE, *supra* note 2, at 5.

<sup>202</sup> NECC AND AMERIDOSE, *supra* note 2, at 13; *see also* U.S. FOOD AND DRUG ADMIN ADVERSE EVENT REPORTING SYSTEM (FAERS) (June 25, 2007).

<sup>203</sup> NECC AND AMERIDOSE, *supra* note 2, at 13; *see also* FDA Warning Letter, *supra* note 197, at 13.

<sup>204</sup> Memorandum from Consumer Safety Officer, New Orleans Dist. Off., FDA, to Supervisory Consumer Safety Officer (Jan. 9, 2008) (memorandum is accidentally dated 2007); *see also*

of increased fibromyalgia pain and suffered severe flu-like symptoms after receiving injections of the drug.<sup>205</sup> By June 2008, the FDA had received additional complaints regarding betamethasone made by NECC.<sup>206</sup>

On October 9, 2008, while the FDA considered how to respond to NECC's January 2007 response letter, the FDA received a complaint stating that a patient had been hospitalized after intravenous administration of phosphatidylcholine made by NECC.<sup>207</sup> The patient vomited, urinated blood, could not swallow food or liquid, and required emergency care for blood clots in his arm and hand.<sup>208</sup> On October 31, 2008, the FDA replied to NECC's response letter according to CPG 2002, but did not return to inspect NECC until after the fungal meningitis crisis had erupted in 2012.<sup>209</sup> Toward the end of 2009, the FDA received complaints regarding NECC's solicitation and distribution of erythromycin without patient-specific prescriptions,<sup>210</sup> as well as NECC's sale of sodium tetradecyl sulfate to a physician in North Carolina for use in treating varicose veins.<sup>211</sup>

Since February 2003, the FDA agreed that the state of Massachusetts would take the lead in overseeing the compounding issues associated with NECC. The FDA had long suspected that NECC was operating outside "traditional" compounding, and by 2011 the agency had evidence that NECC was operating more like a drug manufacturer and was convinced that it functioned as a drug manufacturer.<sup>212</sup>

During this period, the FDA continued to grapple with the implications of the Circuit Court split. The FDA continued to assert that compounded drugs fell within the FDCA's definition of "new drugs" and subjected compounded drugs to the FDCA's new drug requirement by applying CPG 2002 outside of the Fifth Circuit. However, because of

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NECC AND AMERIDOSE, *supra* note 2, at 14.

<sup>205</sup> Memorandum to Consumer Safety Officer, *supra* note 204; *see also* NECC AND AMERIDOSE, *supra* note 2, at 14.

<sup>206</sup> NECC AND AMERIDOSE, *supra* note 2, at 15.

<sup>207</sup> U.S. FOOD AND DRUG ADMIN., CONSUMER COMPLAINT/INJURY REPORT at 1 (Oct. 9, 2008); NECC AND AMERIDOSE, *supra* note 2, at 17.

<sup>208</sup> FDA CONSUMER COMPLAINT/INJURY REPORT, *supra* note 207.

<sup>209</sup> NECC AND AMERIDOSE, *supra* note 2, at 17.

<sup>210</sup> E-mail from Kathleen R. Anderson to Samia Nasr, Div. of New Drugs and Labeling Compliance (Sept. 14, 2009, 3:26 EST); *see also* E-mail from Samia Nasr to Kathleen R. Anderson (Sept. 14, 2009, 3:34 EST); NECC AND AMERIDOSE, *supra* note 2, at 19.

<sup>211</sup> E-mail from Compliance Officer, New England Dist. Off., FDA (Sept. 24, 2009, 3:40 EST); *see also* NECC AND AMERIDOSE, *supra* note 2, at 19.

<sup>212</sup> NECC AND AMERIDOSE, *supra* note 2, at 20.

uncertainty over the scope of federal authority, FDA oversight of compounded drugs remained minimal.<sup>213</sup>

*B. FDA Oversight of Ameridose*

Ameridose, NECC's sister company, also had a checkered past. The common ownership and management of NECC and of Ameridose was a factor in the FDA's decision to take action against both. Ameridose was registered with the FDA—contrary to NECC—as a manufacturer since September 2006,<sup>214</sup> and advertised that it met both USP compounding standards and cGMP requirements.<sup>215</sup> In addition, Ameridose was also registered in Massachusetts as a retail pharmacy, and it had Drug Enforcement Administration (DEA) licenses as a manufacturer and as a retail pharmacy for controlled substances.<sup>216</sup>

Within a year of Ameridose's registration, the FDA received a complaint through the MedWatch system alleging that Ameridose was manufacturing unapproved intravenous solutions that were dispensed without a valid prescription.<sup>217</sup> Prior to its first inspection in December 2007, the FDA noted Ameridose's connection with NECC, and it sought information regarding the business relationship and leadership structure of Ameridose and of NECC.<sup>218</sup>

In July 2008, a second FDA inspection determined that Ameridose was a “high risk” facility that had significantly expanded its business operations since the first inspection.<sup>219</sup> The inspection found that Ameridose marketed over 600 products, including antibiotics, 15 Class II, one Class III, two Class IV, and many Class VI products.<sup>220</sup> Ameridose's customers included approximately 500 hospital pharmacies located in

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<sup>213</sup> NECC AND AMERIDOSE, *supra* note 2, at 21.

<sup>214</sup> FDA Timeline, *supra* note 157, at 2; *see* NECC AND AMERIDOSE, *supra* note 2, at 21.

<sup>215</sup> NECC AND AMERIDOSE, *supra* note 2, at 21.

<sup>216</sup> NECC AND AMERIDOSE, *supra* note 2, at 21; *see also* U.S. FOOD AND DRUG ADMIN., ESTABLISHMENT INSPECTION REPORT at 1 (Jan. 22, 2008) [hereinafter ESTABLISHMENT INSPECTION REPORT].

<sup>217</sup> Inspection Request from Staff Fellow, Compounding Team, DNDLC, Off. of Compliance, CDER, FDA, to Michael Kravchuk, Dir., Investigations Branch, New England Dist. Off., FDA at 1 (May 21, 2007); *see also* NECC AND AMERIDOSE, *supra* note 2, at 22.

<sup>218</sup> NECC AND AMERIDOSE, *supra* note 2, at 23.

<sup>219</sup> NECC AND AMERIDOSE, *supra* note 2, at 24.

<sup>220</sup> NECC AND AMERIDOSE, *supra* note 2, at 24; *see also* U.S. FOOD AND DRUG ADMIN., ESTABLISHMENT INSPECTION REPORT at 4 (Aug. 22, 2008) (page numbers correspond with narrative report attachment).

forty-nine states.<sup>221</sup> Ameridose shipped 75 percent of its manufactured or repackaged products outside Massachusetts without patient-specific prescriptions.<sup>222</sup>

The second inspection included testing of fentanyl, an injectable narcotic more powerful than morphine.<sup>223</sup> Test results showed that the product exceeded potency standards.<sup>224</sup> The FDA informed Gregory Conigliaro, co-owner of Ameridose, that the compounded fentanyl product was “adulterated” because it had failed to meet federal potency standards.<sup>225</sup> Nevertheless, the FDA did not issue a Warning Letter to Ameridose due to conflicting court holdings.<sup>226</sup>

In view of the Circuit split, the FDA debated how to enforce the law. It considered applying section 503A only in the Fifth Circuit and exercising enforcement discretion elsewhere. It also considered uniformly applying CPG 2002 nationwide, and exercising enforcement discretion regarding compounding pharmacies.<sup>227</sup> Eventually, the FDA opted for the latter approach but decided that it needed to establish a clear framework and guidance document that distinguished between pharmacy compounding and drug manufacturing. Unfortunately, the FDA had not completed the framework and guidance before the NECC fungal meningitis outbreak.

As the FDA developed new compounding guidance, federal enforcement of Ameridose stalled. In October 2009, the FDA received an anonymous email alleging that Ameridose had directed a facility that was responsible for monitoring quality and testing the purity of its drugs to change the test reports and to force the employees to forge test results.<sup>228</sup> In response, the FDA prepared to inspect Ameridose.<sup>229</sup> In early June 2010, the agency received yet another complaint from a manufacturer related to Ameridose’s admixing and distribution of nicardipine IV injection products.<sup>230</sup> Since the FDA could not determine whether

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<sup>221</sup> NECC AND AMERIDOSE, *supra* note 2, at 5.

<sup>222</sup> NECC AND AMERIDOSE, *supra* note 2, at 3.

<sup>223</sup> ESTABLISHMENT INSPECTION REPORT, *supra* note 216.

<sup>224</sup> ESTABLISHMENT INSPECTION REPORT, *supra* note 216; *see* NECC AND AMERIDOSE, *supra* note 2, at 24.

<sup>225</sup> NECC AND AMERIDOSE, *supra* note 2, at 25.

<sup>226</sup> NECC AND AMERIDOSE, *supra* note 2, at 26.

<sup>227</sup> NECC AND AMERIDOSE, *supra* note 2, at 27.

<sup>228</sup> NECC AND AMERIDOSE, *supra* note 2, at 28.

<sup>229</sup> NECC AND AMERIDOSE, *supra* note 2, at 28.

<sup>230</sup> NECC AND AMERIDOSE, *supra* note 2, at 29.

Ameridose was operating outside of CPG 2002,<sup>231</sup> it did not take immediate action.<sup>232</sup>

In July 2010, the FDA received an anonymous complaint from an Ameridose pharmacist alleging that the firm had compounded contaminated batches of succinylcholine because it did not follow cGMP.<sup>233</sup> The FDA also received a MedWatch report stating that a nurse, who had administered a syringe of dextrose that was 50 percent made by Ameridose, noticed a white precipitate along the plunger's base.<sup>234</sup> In August 2010, the same Ameridose informant alleged that one of the clean rooms had mold growth.<sup>235</sup> Four days later, the informant reported that mold was also found in the hood space where the operations took place.<sup>236</sup> Without a warrant the FDA was unable to inspect the company and determine whether Ameridose was operating outside of CPG 2002.<sup>237</sup>

On January 14, 2011, the FDA was informed that a settlement had been reached between Ameridose and those who filed the commercial complainant in the nicardipine matter.<sup>238</sup> One month later, the FDA received a medication error report about a photocopied Ameridose label of a sodium chloride product compounded and distributed by Ameridose. The Ameridose label did not indicate that the sodium chloride was sterile.<sup>239</sup> The FDA did not conduct an inspection of Ameridose until the agency issued guidance asserting federal authority under CPG 2002.<sup>240</sup> The agency also planned to re-inspect Ameridose after issuance of the new guidance.<sup>241</sup>

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<sup>231</sup> NECC AND AMERIDOSE, *supra* note 2, at 30.

<sup>232</sup> NECC AND AMERIDOSE, *supra* note 2, at 30.

<sup>233</sup> Memorandum of Teleconference between Redaction and Compliance Officer, New England Dist. Off., FDA (Jul. 13, 2010); *see also* NECC AND AMERIDOSE, *supra* note 2, at 29.

<sup>234</sup> NECC AND AMERIDOSE, *supra* note 2, at 30; *see also* U.S. FOOD AND DRUG ADMIN, MEDWATCH REPORT (Jul. 23, 2010).

<sup>235</sup> Memorandum of Teleconference between Redaction and Compliance Officer, New England Dist. Off., FDA, at 1 (Aug. 16, 2010); *see also* NECC AND AMERIDOSE, *supra* note 2, at 30.

<sup>236</sup> NECC AND AMERIDOSE, *supra* note 2, at 31.

<sup>237</sup> NECC AND AMERIDOSE, *supra* note 2, at 31.

<sup>238</sup> NECC AND AMERIDOSE, *supra* note 2, at 33.

<sup>239</sup> NECC AND AMERIDOSE, *supra* note 2, at 33.

<sup>240</sup> NECC AND AMERIDOSE, *supra* note 2, at 10.

<sup>241</sup> E-mail from Consumer Safety Officer, Compounding & Pharmacy Practices Team, Div. of Prescription Drugs, Off. of Unapproved Drugs & Labeling Compliance (OUDLC), Off. of Compliance, CDER, FDA, to Consumer Safety Technician, OUDLC (Sept. 15, 2011, 3:46 EST). By September 2011, the Office of Compliance appears to have been restructured, resulting in the Compounding Team, formerly within the Division of New Drugs and Labeling Compliance, being renamed the Compounding and Pharmacy Practices Team within the Office of Unapproved Drugs and Labeling Compliance, Division of Prescription Drugs. NECC AND AMERIDOSE, *supra* note

While the FDA focused on developing the new guidance, complaints regarding Ameridose continued to be reported. In November 2010, the California Health Department and Board of Pharmacy reported that Ameridose was shipping repackaged succinylcholine products without packaging inserts and with significantly different expiration dates than the branded products.<sup>242</sup> The FDA also received an adverse event report regarding Ameridose products in which three women complained of poor pain control after receiving epidural fentanyl injections while in labor.<sup>243</sup>

In January 2012, the FDA received additional reports indicating that fentanyl was distributed by Ameridose without clear labeling and almost resulted in a nurse administering 100 mcg of the drug instead of fifty mcg to a patient.<sup>244</sup> The FDA also received an adverse event report involving an Ameridose heparin product. Hospital lab tests revealed that the heparin bags in fact did not contain heparin.<sup>245</sup> Despite these complaints, the FDA delayed action until after it drafted the new guidelines.

By late September 2012, NECC had already shipped two of the three batches of contaminated methylprednisolone acetate to facilities across the country, leading to the fatal fungal meningitis outbreak.<sup>246</sup> On October 10, 2012, after it was determined that NECC was at the epicenter of the crisis, the FDA, along with Massachusetts authorities began inspection of Ameridose.<sup>247</sup>

By November 1, 2012, the FDA announced that Ameridose was conducting a voluntary recall of all of its unexpired products in circulation based on the preliminary results of the FDA's ongoing inspection, which had documented a lack of sterility assurance.<sup>248</sup> On November 9, 2012, the FDA sent Gregory Conigliaro a Warning Letter documenting problems the agency observed during the October 10 inspection.<sup>249</sup> The

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2, at 34.

<sup>242</sup> NECC AND AMERIDOSE, *supra* note 2, at 36.

<sup>243</sup> U.S. FOOD AND DRUG ADMIN ADVERSE EVENT REPORTING SYSTEM (FAERS) (Nov. 17, 2011); *see also* NECC AND AMERIDOSE, *supra* note 2, at 36.

<sup>244</sup> U.S. FOOD AND DRUG ADMIN ADVERSE EVENT REPORTING SYSTEM (FAERS), <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082193.htm> (last visited Feb. 26, 2018).

<sup>245</sup> *Id.*

<sup>246</sup> NECC AND AMERIDOSE, *supra* note 2, at 38

<sup>247</sup> NECC AND AMERIDOSE, *supra* note 2, at 38.

<sup>248</sup> Warning Letter from FDA Pub. Health Serv. to Barry J. Cadden, Director of Pharmacy and Owner NECC (Dec. 4, 2006).

<sup>249</sup> U.S. FOOD AND DRUG ADMIN., DEP'T OF HEALTH AND HUM. SERVICES FORM 483 (Nov. 9, 2012).

Warning Letter stated that the firm failed: 1) to test finished products for potency; 2) to investigate complaints for ineffective products; 3) to investigate violations of their own environmental sampling plan; and 4) to adequately maintain equipment and facilities used to manufacture sterile drug products.<sup>250</sup> FDA uncertainty over its legal authority prevented the agency from initiating enforcement actions sooner.<sup>251</sup> The FDA's legal authority for pharmacy compounding was limited, unclear, and untested.<sup>252</sup> These factors impeded the FDA's ability to act despite the activities of NECC and Ameridose creating mounting concerns for patient safety and for public health.<sup>253</sup>

### C. NECC Violates Legal and Quality Standards

At the time of the NECC crisis, section 503A of the FDCA exempted drug products compounded by a pharmacist or physician on a customized basis for an individual patient from three key provisions of the FDCA: 1) the adulteration provision of section 501 (a)(2)(B) (concerning the cGMP requirements); 2) the misbranding provision of section 502(f)(1) (concerning the labeling of drugs with adequate directions for use); and 3) the new drug provision of section 505 (concerning the approval of drugs under NDAs or ANDAs). To qualify for these exemptions, section 503A requires that the medication be compounded by:

1) "a licensed physician, on the prescription order for such individual patient made by a licensed physician or other licensed professional authorized by State law to prescribe drugs"; or

2) "a licensed pharmacist or licensed physician in limited quantities before the receipt of a valid prescription order for such individual patient"; and centered "on a history of the licensed pharmacist or licensed physician receiving valid prescription orders for the compounding of the drug product, which orders have been generated solely within

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<sup>250</sup> Elizabeth Weise, *FDA finds contamination at Ameridose*, USA TODAY (Nov. 13, 2012, 5:21 PM), <http://www.usatoday.com/story/news/nation/2012/11/12/fda-ameridose-meningitis/1700589/>; see also NECC AND AMERIDOSE, *supra* 2, at 39.

<sup>251</sup> *The Fungal Meningitis Outbreak: Could It Have Been Prevented? Hearing Before the Subcomm. on Oversight & Investigations of the H. Comm. on Energy & Commerce*, 112th Cong. 10 (Nov. 14, 2012) (statement of Margaret Hamburg, Comm. Of food and Drug Admin., Dep't of Health and Hum. Services) [hereinafter Hamburg Statement], <https://web.archive.org/web/20121203012007/https://www.fda.gov/NewsEvents/Testimony/ucm327664.htm>.

<sup>252</sup> *Id.* at 74; see generally Energy and Commerce Committee, <http://energycommerce.house.gov/hearing/fungal-meningitis-outbreak-could-it-have-been-prevented> (last visited Feb. 26, 2018).

<sup>253</sup> NECC AND AMERIDOSE, *supra* note 2, at 39.

an established relationship” between the licensed professional and “such individual patient for whom the prescription order will be provided.”<sup>254</sup>

In legal filings, the government provided evidence that NECC engaged in fraudulent practice by using fake patient names, such as, the names of celebrities, fictional characters, doctors, and medical staff, to create fraudulent prescriptions for drugs.<sup>255</sup> For instance, NECC used names, such as, Big Baby, Jesus, Fat Albert, Wonder Woman, Pee-wee Herman, Freddie Mae, Fannie Mac, Silver Surfer, Tony Tiger, Coco Puff, Harry Potter, Ned Flanders, Flash Gordon, Jimmy Carter, Bill Clinton, Jennifer Lopez, or Dale Earnhardt.<sup>256</sup>

In another instance, NECC used the names of patients supplied by NECC’s customers to create fraudulent prescriptions for drugs, or shipped drugs to NECC’s customers without any patient names, and then used the names of patients received after the drug shipments to create fraudulent prescriptions for those or subsequent orders.<sup>257</sup> In one particular situation, NECC instructed staff to create 300 fraudulent prescriptions for the surgical patients of a Massachusetts hospital and later submitted a response to a Massachusetts Board of Pharmacy inquiry, by including in an attachment “[t]hree hundred patient-specific transcribed prescriptions #132023 7 -#1320536 which are retained per [NECC’s standard operating procedure].”<sup>258</sup>

Compounding pharmacies were also subject to the standards set by the USP Convention for drug purity, quality or identification.<sup>259</sup> All compounding personnel had to comply with USP Chapter 797, which set standards to guarantee the sterility of drugs in order to ensure safety.<sup>260</sup> Among many requirements, USP Chapter 797 required that

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<sup>254</sup> FDCA § 503A.

<sup>255</sup> Grand Jury Charge at 42, *United States v. Cadden*, 1:14-cr-10363-RGS-1 (D. Mass.). Some fictitious names shared a common theme such as Bud Weiser, Richard Coors, Michael Keystone, Adam Foster, Samuel Adams, John Killian, or Raymond Rollingrock. *Id.* At one point, one of the defendants commented in an email to a sales representative that the “facility uses bogus patient names that are just ridiculous,” to which the sales representative acquiesced, “[t]hese are RIDICULOUS.” *Id.*

<sup>256</sup> *Id.* at 44-46.

<sup>257</sup> *Id.* at 39.

<sup>258</sup> *Id.* at 47.

<sup>259</sup> PHARMACOPEIAL CONVENTION, (797), *supra* note 41, at 4. This scientific organization publishes those standards in the USP. In Massachusetts, all licensed pharmacists are required to follow the standards set forth in the USP per section 9.01(3) of Title 247 of the Code of Massachusetts Regulations. CODE OF PROF’L CONDUCT; PROF’L STANDARDS FOR REGISTERED PHARMACISTS, PHARMACIES AND PHARMACY DEPARTMENTS § 9.01(3) (BD. OF REGISTRATION IN PHARMACY 2014).

<sup>260</sup> PHARMACOPEIAL CONVENTION, (797), *supra* note 41, at 27.

the drugs be exposed to steam at 121°C under a pressure of one atmosphere for twenty to sixty minutes to ensure sterilization.<sup>261</sup> USP Chapter 797 further required that the sterilization process be verified through the use of a biological indicator and that compounding pharmacies document conditions and durations that specific drugs were sterilized.<sup>262</sup> NECC repeatedly failed to implement and strictly adhere to these procedures. For instance, NECC routinely autoclaved the drugs for fifteen to seventeen minutes instead of twenty to sixty minutes required by USP Chapter 797, and never verified the effectiveness of the sterilization.<sup>263</sup> NECC violated USP Chapter 797 by using expired ingredients and stock solutions in compounding sterile drugs, mixing stock solutions from different drug batches, and failing to clean and disinfect clean rooms.<sup>264</sup>

## VI. State Response to the Crisis

### A. Hobbled State Oversight

Many states have insufficient resources or staff to adequately inspect and oversee licensed pharmacies, and this creates problems for their own citizens and citizens of the other states where compounding pharmacies sell medications.<sup>265</sup> Until the NECC crisis, states typically relied on the jurisdictions where the pharmacies were located to license and regulate drug compounding.<sup>266</sup>

State Boards of Pharmacy have also lacked consistent inspection practices, thereby hampering state oversight.<sup>267</sup> Pharmacy organizations have indicated that there is no assurance that non-resident pharmacies receive the same level of oversight as resident pharmacies since the frequency of pharmacy inspections and the qualifications of the inspectors can vary drastically among non-resident pharmacies.<sup>268</sup>

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<sup>261</sup> PHARMACOPEIAL CONVENTION, (797), *supra* note 41, at 10.

<sup>262</sup> PHARMACOPEIAL CONVENTION, (797), *supra* note 41, at 10.

<sup>263</sup> PHARMACOPEIAL CONVENTION, (797), *supra* note 41, at 13.

<sup>264</sup> PHARMACOPEIAL CONVENTION, (797), *supra* note 41, at 12.

<sup>265</sup> A discussion on the states' resource constraints and their ability to oversee drug compounding can also be found in GAO REPORT, *supra* note 12, at 25-26.

<sup>266</sup> GAO REPORT, *supra* note 12, at 25.

<sup>267</sup> GAO REPORT, *supra* note 12, at 25.

<sup>268</sup> GAO REPORT, *supra* note 12, at 25. In response, some states are beginning to regulate nonresident pharmacies. *Id.* at 28. For instance, California, Florida, and Iowa require licensure or registration of nonresident pharmacies that provide services in the state. *Id.* These three states also require nonresident pharmacies applying for a license or registration to have a current license, permit, or registration issued by the regulatory body of the pharmacies' home state. *Id.*

State Boards of Pharmacy have also failed to make their inspection information readily available for review, thereby making it harder for state regulators to ensure safety, particularly for non-resident pharmacies.<sup>269</sup> With a few exceptions,<sup>270</sup> state enforcement records regarding safety have not been made public or readily accessible for review. Most State Boards of Pharmacy websites do not allow for keyword searches, which prevents the public from easily and efficiently locating or downloading enforcement records associated with violations regarding pharmacies or compounded drugs in a certain jurisdiction.<sup>271</sup> Moreover, publicly available information, such as state enforcement activities, only include traditional types of violations by individual pharmacies or pharmacists, such as billing violations, failure to have a licensed pharmacist onsite, or the distribution of controlled substances by the falsification of prescriptions.<sup>272</sup>

### *B. States' Response After the Fungal Meningitis Outbreak*

Immediately after the NECC outbreak, the FDA convened a national meeting with the leaders of each state's Board of Pharmacy. The agency sought input regarding state oversight of compounding pharmacies.<sup>273</sup>

In collaboration with the National Association of Boards of Pharmacy (NABP) and other national pharmacy organizations, some states such as California, Florida, and Iowa have increased inspections.<sup>274</sup> They developed a specific inspection program for sterile drug compounders located outside of the state that dispense drugs in the state. They also drafted legislation requiring their Boards of Pharmacy to conduct onsite inspections prior to licensing a pharmacy for exporting drug products.<sup>275</sup>

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<sup>269</sup> Office of Congressman Edward J. Markey (D-Mass.), *Compounding Pharmacies: Compounding Risk*, 10 (Oct. 29, 2012), [https://www.snmami.org/files/docs/Compounding%20Pharmacies%20-%20Compounding%20Risk%20FINAL\\_0.pdf](https://www.snmami.org/files/docs/Compounding%20Pharmacies%20-%20Compounding%20Risk%20FINAL_0.pdf).

<sup>270</sup> *Id.*

<sup>271</sup> Instead of keyword search capabilities, state enforcement action records relating to pharmacies are often limited to alphabetical or temporal lists, or summaries of violations that are not themselves searchable. *Id.* at 11. These lists in many instances lack sufficient information to understand the nature of the violation by pharmacies. *Id.*

<sup>272</sup> *Id.* at 3.

<sup>273</sup> Open Letter from Dr. Hamburg, Commissioner of Fed. Food and Drug Admin., to State Boards of Pharmacy (Jan. 8, 2014) [hereinafter Hamburg Letter]; Pontikes, *supra* note 1, at 15.

<sup>274</sup> See generally GAO REPORT, *supra* note 12.

<sup>275</sup> GAO REPORT, *supra* note 12, at 20. The NABP instituted a Compounding Action Plan

California enacted legislation prohibiting resident and non-resident pharmacies from compounding or dispensing any sterile drugs in California unless they possess a sterile compounding pharmacy license; and it required the California State Board of Pharmacy to inspect pharmacies prior to granting such licenses.<sup>276</sup> The license requires that: 1) resident and non-resident pharmacies report adverse events related to compounded drugs to both the California State Board of Pharmacy and the FDA's adverse event reporting system (MedWatch); and 2) all pharmacies submit a list of all sterile medications compounded during the previous twelve months.<sup>277</sup>

The California law exempts certain pharmacies accredited by a private accreditation agency approved by the California State Board of Pharmacy.<sup>278</sup> Licensed pharmacies are subject to annual inspections prior to license renewal. Non-resident pharmacies must provide a copy of a recent inspection report issued by the pharmacy's licensing agency or a private accrediting agency approved by the California State Board of Pharmacy, demonstrating that the pharmacy complies with regulations regarding the compounding of injectable sterile drug products.

Florida's Board of Pharmacy issued an emergency rule following the NECC crisis, requiring resident and non-resident pharmacies to notify the State Board of Pharmacy of all compounding activities.<sup>279</sup> Prior

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(CAP) to identify and inspect compounding pharmacies. *Id.* at 24. Initially, the NABP drew on lists of pharmacies and inspection results obtained from the Iowa non-resident inspection program. *Id.* The NABP intends to collect data regarding the scope of compounding operations from all the states, and follow with inspections of the compounding pharmacies. *Id.* The NABP asked all states to identify any known or suspected compounding pharmacies in their state that are not on the Iowa list. *Id.*

<sup>276</sup> Cal. Bus. & Prof. Code §§ 4127.1, 4127.2.

<sup>277</sup> *Id.*; see GAO REPORT, *supra* note 12, at 20 (discussing California and other state law).

<sup>278</sup> Cal. Bus. & Prof. Code §§ 4127.1-4127.2. Resident pharmacies operated by entities that are licensed by either the board or the California Department of Health and nonresident pharmacies operated by entities that are licensed as a hospital, home health agency, or a skilled nursing facility are eligible for such exemption. *Id.* In contrast to current law, which imposes special licensure requirements only on pharmacies compounding injectable sterile drugs, this proposed legislation would require pharmacies compounding all types of sterile drugs to meet such requirements. *Id.*; GAO REPORT, *supra* note 12, at 21.

<sup>279</sup> See Rule No. 64B16ER12-1, Immediate Notification of Compounding Status and Inspections, 38 Fla. Admin. Reg. 5183-5184 (Nov. 27, 2012). The GAO Report states:

Specifically, Florida's emergency rule required resident pharmacies with state pharmacy permits and nonresident pharmacies registered with the state to immediately notify the board of their sterile and non-sterile compounding activities, the types of drugs they compound, and whether they compound drugs in bulk. In addition, the emergency rule required Florida's board of pharmacy to use the information on compounding activities to place a high priority on inspecting high-risk pharmacies such as those that compound sterile drugs. The emergency rule also required all nonresident registered

to the emergency rule, the state did not know the number of resident pharmacies compounding drugs, or which non-resident pharmacies imported non-sterile or sterile compounded drugs. Following the emergency rule, the state learned that 12 percent of pharmacies compounded sterile products, such as injectable and ophthalmic solutions; 32 percent of pharmacies performing sterile compounding were non-resident pharmacies; and 55 percent of the responding pharmacies compounded non-sterile products, such as ointments or tablets.<sup>280</sup> The Board of Pharmacy relied on this information to prioritize risk-based inspections.<sup>281</sup>

The NABP has inspected drug compounders licensed by Iowa as non-resident pharmacies.<sup>282</sup> The inspections revealed that certain non-resident pharmacies compounded drugs that violated Iowa regulations.<sup>283</sup> In response, the Iowa Board of Pharmacy initiated disciplinary actions against those out-of-state pharmacies.<sup>284</sup>

Other states have followed the lead of California, Florida, and Iowa. At least eighteen states have proposed or passed new legislation addressing compounded drugs or state oversight over compounding practices.<sup>285</sup>

### VII. *The Drug Quality and Security Act of 2013*

Investigations of the NECC crisis identified several problems with industry practice and existing law.<sup>286</sup> Federal and state responsibility

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pharmacies to provide a copy of their last two inspection reports as provided by the state in which the pharmacies are physically located and licensed.

GAO Report, *supra* note 12, at 22 n.37.

<sup>280</sup> GAO REPORT, *supra* note 12, at 22; *see also* DIV. OF MED. QUALITY ASSUR., FLA. DEP'T OF HEALTH, FLORIDA BOARD OF PHARMACY COMPOUNDING SURVEY REPORT (2013).

<sup>281</sup> DIV. OF MED. QUALITY ASSUR., FLA. DEP'T OF HEALTH, FLORIDA BOARD OF PHARMACY COMPOUNDING SURVEY REPORT (2013); *see also* Rule No. 64B16ER12-1, Immediate Notification of Compounding Status and Inspections, 38 Fla. Admin. Reg. 5183-5184 (Nov. 27, 2012).

<sup>282</sup> GAO REPORT, *supra* note 12, at 23.

<sup>283</sup> GAO REPORT, *supra* note 12, at 23.

<sup>284</sup> GAO REPORT, *supra* note 12, at 23.

<sup>285</sup> *See 2014 State Compounding Legislation Tracker*, INT'L ACAD. COMPOUNDING PHARMACISTS (2014), <http://c.ymcdn.com/sites/www.iacprx.org/resource/resmgr/imported/20Weekly%20of%20State%20Legislation%2001282014-1.pdf>. These efforts by the states were echoed by industry organizations, such as the NABP. Pontikes, *supra* note 1. For example, the NABP convened a meeting in November 2012 with executive directors of the State Boards of Pharmacy, and with a goal of developing a system to identify and correct the systemic failures that led to the NECC outbreak. *Id.*

<sup>286</sup> PEW CHARITABLE TRUSTS, NATIONAL ASSESSMENT OF STATE OVERSIGHT OF STERILE DRUG COMPOUNDING (Feb. 2016), [http://www.pewtrusts.org/~media/2016/02/national\\_assessment\\_of\\_state\\_of\\_sterile\\_drug\\_compounding.pdf](http://www.pewtrusts.org/~media/2016/02/national_assessment_of_state_of_sterile_drug_compounding.pdf).

regarding compounding pharmacies needed to be clarified. Inconsistent federal circuit court decisions had required the FDA to apply different standards across various regions.<sup>287</sup> State oversight varied based on local law and state resources.<sup>288</sup> The FDA also lacked timely and reliable information relayed from state inspections and enforcement.<sup>289</sup> Furthermore, many states and purchasers incorrectly believed that the FDA had approved drugs and inspected facilities that advertised themselves as “FDA registered.”<sup>290</sup> The result was regulatory gaps and inadequate public health protection.<sup>291</sup>

Senate and House of Representatives hearings investigated ways to improve oversight of compounding pharmacies.<sup>292</sup> FDA officials testified in favor of legislation that granted the FDA explicit authority over “non-traditional” compounding.<sup>293</sup> The statute does not define “traditional” compounding; however, FDA officials use the term to signify pharmacies that compound a drug “for an identified individual patient based on the receipt of a valid prescription order.”<sup>294</sup>

Non-traditional compounding falls between traditional compounding and manufacturing, particularly the production of sterile product produced in advance without an individual patient prescription that are shipped across state lines.<sup>295</sup> Commissioner Hamburg testified that non-traditional compounding should be identified according to the FDA’s CPG 1992, CPG 2002, and based on four factors: 1) the type of product or compounding activity; 2) the volume compounded; 3) whether the compounding occurred prior to receipt of a “patient-specific” prescription; and 4) whether the medications were shipped into interstate commerce.<sup>296</sup>

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<sup>287</sup> *Id.* at 2-3

<sup>288</sup> *Id.* at 1.

<sup>289</sup> *See generally id.*

<sup>290</sup> GAO REPORT, *supra* note 12, at 27.

<sup>291</sup> *See generally id.*

<sup>292</sup> CRS REPORT R43038, *supra* note 44, at 45.

<sup>293</sup> Hamburg Letter, *supra* note 273.

<sup>294</sup> GAO REPORT, *supra* note 12, at 37; *see also* Pontikes, *supra* note 1.

<sup>295</sup> GAO REPORT, *supra* note 12, at 12; *see, e.g., Pharmaceutical Compounding: Proposed Legislative Solution: Hearing Before the S. Comm. on Health, Education, Labor & Pensions*, 113th Cong. (2013) (statement of Janet Woodcock, M.D., Director, Center for Drug Eval. & Research, Food & Drug Admin.); *see also* Hamburg Statement, *supra* note 251.

<sup>296</sup> *A Continuing Investigation Into the Fungal Meningitis Outbreak and Whether it Could Have Been Prevented: Hearing Before the Subcomm. on Oversight & Investigations of the H. Comm. on Energy & Commerce*, 113th Cong. (2013) (statement of Dr. Margaret A. Hamburg, Comm’r, Food and Drug Admin.); *see also* Pontikes, *supra* note 1.

The Drug Quality and Security Act (DQSA), enacted in November 2013, includes two parts: Title I, the Compounding Quality Act (CQA); and Title II, the Drug Supply Chain Security Act (DSCSA).<sup>297</sup>

A. *The Compounding Quality Act*

The CQA authorizes the FDA to oversee non-traditional compounding pharmacies, those that compound and ship large quantities of sterile drugs that are willing to submit to its jurisdiction. However, under the CQA, compliance with the new standards apply only to pharmacies that voluntarily register as “outsourcing facilities.”<sup>298</sup>

1. *Outsourcing Facilities for Certain Non-Traditional Compounding*

The CQA creates the new legal category *outsourcing facilities* under section 503B to the FDCA.<sup>299</sup> Qualifying pharmacies can register annually and be regulated as outsourcing facilities.<sup>300</sup> Pharmacies that

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<sup>297</sup> Drug Quality and Security Act, Pub. L. No. 113-54, 127 Stat. 587 (2013). Since Congress enacted the DQSA, sixty-seven compounding facilities have registered with the FDA as outsourcing facilities and are subject to increased quality standards and federal oversight. See U.S. FOOD AND DRUG ADMIN., FDA’S HUMAN DRUG COMPOUNDING PROGRESS REPORT (Jan. 2017), <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/ucm536549.pdf>. The CQA has also enabled the FDA to increase its inspections of compounding facilities and permitted the agency to respond to compounders that violate the FDCA. FDA COMPOUNDING PROGRESS REPORT, *supra*, at 10. The FDA has issued seven final guidance documents, eighteen draft guidance documents, one final rule, two proposed rules, and a draft memorandum of understanding with the states. *Id.* The FDA has worked closely with the states to share information and coordinate regulatory efforts. *Id.* Since November 27, 2016, the FDA has: 1) conducted eighty-five inspections of outsourcing facilities—issuing many Form FDA 483s when it found violations of the FDCA; 2) issued more than 130 warning letters advising compounders of significant violations of sections 503A or 503B; 3) issued more than thirty letters related to inspectional findings to state regulatory agencies so that states could ensure that violators brought their activities into compliance; and 4) overseen the recall of up to 100 compounded drugs due to unsanitary facility conditions or sub- or super-potent drug products. *Id.* Compounders that do not come into compliance may be subject to enforcement action, such as seizure, injunction, or criminal prosecution. *Id.* In addition, the FDA has also worked with the Department of Justice on many civil and criminal enforcement actions regarding violations of the FDCA. These steps have reduced risks and improved safety. *Id.*; Drug Quality and Security Act (DQSA), tit. I, § 102; FDCA § 503B(a)(1) (2013); DQSA, tit. II, § 201.

<sup>298</sup> DQSA, tit. I, § 102; FDCA § 503B.

<sup>299</sup> DQSA, tit. I, § 102; FDCA § 503B(a)(1); see also U.S. FOOD AND DRUG ADMIN., REGISTERED OUTSOURCING FACILITIES (Feb. 10, 2017), <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm.htm>.

<sup>300</sup> DQSA, tit. I, § 102; FDCA § 503B. Under FDCA § 503B(b), the FDA can deem compounded drugs misbranded if they were produced by an outsourcing facility that has not registered and paid its annual registration fee. See FDCA § 503B(b)(1).

do not register must either meet the requirements for traditional pharmacies under section 503A, or for manufacturers under sections 502(f)(1), 505, and 582. They must inform the FDA of certain activities, most notably, if they intend in the following year to compound drugs appearing on the FDA's drug shortage list or compound sterile drugs from bulk substances.<sup>301</sup> Outsourcing facilities can also maintain a state pharmacy license.<sup>302</sup>

Outsourcing facilities compound sterile drugs under the direct supervision of a licensed pharmacist.<sup>303</sup> They are not required to obtain prescriptions for individual patients, but they are only allowed to compound drugs that the FDA authorizes and must comply with cGMPs and certain reporting and labeling requirements.<sup>304</sup> They are exempt from the FDCA standard for new drug approvals each time they compound a drug,<sup>305</sup> as well as certain labeling requirements designed to ensure adequate directions for the drug's use.<sup>306</sup>

Section 503B restricts the drugs that outsourcing facilities can prepare, the bulk substances that they can use, and it regulates their operations.

There are five main restrictions:

- 1) Prohibition on compounding drugs withdrawn from the market for safety or efficacy reasons, or when the FDA indicates present demonstrable difficulties for compounding.<sup>307</sup>
- 2) Prohibition on compounded drugs that are "essentially a copy"

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<sup>301</sup> Pontikes, *supra* note 1; *see* FDCA § 503B(b)(2). According to the FDA's Draft 503B Guidance, the registration process must be completed between October 1 and December 31 of each year and requires the outsourcing facility to provide the name, place of business, unique facility identifier, and a designated point of contact email address. U.S. FOOD AND DRUG ADMIN., DRAFT GUIDANCE: REGISTRATION FOR HUMAN DRUG COMPOUNDING OUTSOURCING FACILITIES UNDER SECTION 503B OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT, 3 (Dec. 2013), <https://www.fda.gov/downloads/guidances/ucm377051.pdf> [hereinafter DRAFT 503B REGISTRATION GUIDANCE]. "This guidance describes the process for submission of registration information for outsourcing facilities. The guidance is intended to facilitate registration as human drug compounding outsourcing facilities. A compounder can elect to register with the FDA as an outsourcing facility under section 503B of the FDCA, as added by the DQSA, Pub. Law No. 113-54 (November 27, 2013)." *Id.*; *see also* U.S. FOOD AND DRUG ADMIN., ELECTRONIC DRUG PRODUCT REPORTING FOR HUMAN DRUG COMPOUNDING OUTSOURCING FACILITIES UNDER SECTION 503B OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT (Dec. 2016).

<sup>302</sup> Pontikes, *supra* note 1; *see* FDCA § 503B(d).

<sup>303</sup> DQSA, tit. I, § 102; FDCA § 503B(a).

<sup>304</sup> Pontikes, *supra* note 1.

<sup>305</sup> DQSA, tit. I, § 102; FDCA § 503B(a); 21 U.S.C. § 355 *et seq.*

<sup>306</sup> DQSA, tit. I, § 102; FDCA § 503B(a).

<sup>307</sup> Pontikes, *supra* note 1; *see* FDCA § 503B(a)(4), (a)(6).

of an FDA-approved drug,<sup>308</sup> defined as: (i) a drug that is identical or nearly identical to an FDA-approved drug or a marketed drug not subject to premarket approval unless FDA finds there is a shortage of the drug at the time of compounding; or (ii) a drug, a component of which is a bulk drug substance that is a component of an approved drug, unless a change in the drug produces a clinical difference for an individual patient.<sup>309</sup>

3) Prohibition on using a bulk drug substance in compounding unless: (i) the bulk drug substance either appears on an FDA approved list or the drug compounded appears on the FDA's drug shortage list;<sup>310</sup> (ii) the bulk substance complies with an applicable USP or NF monograph, or another compendium or pharmacopeia recognized by the FDA;<sup>311</sup> (iii) the bulk drug substance is manufactured by a FDA-registered facility;<sup>312</sup> and (iv) the purity of the bulk drug substance is confirmed by a valid certificate of analysis reflecting purity.<sup>313</sup>

4) Prohibition on acting as wholesalers or distributing compounded drugs for resale,<sup>314</sup> or transfer to other entities.<sup>315</sup>

5) Prohibition on compounding drugs subject to a Risk Evaluation and Mitigation Strategy (REMS) unless the pharmacy has demonstrated to the FDA that it utilizes comparable controls.<sup>316</sup>

The CQA also prohibits: 1) reselling compounded drugs that are labeled "not for resale"; 2) intentionally falsifying a prescription for a compounded drug; 3) failing to report drugs from an outsourcing facility or adverse events; and 4) using advertisements or promotions of compounded drugs that are false or misleading.<sup>317</sup>

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<sup>308</sup> DQSA, tit. I, § 102; FDCA § 503B(a)(5)-(6).

<sup>309</sup> Pontikes, *supra* note 1; *see* FDCA § 503B(d)(2).

<sup>310</sup> DQSA, tit. I, § 102; FDCA § 503B(a)(2)(A).

<sup>311</sup> DQSA, tit. I, § 102; FDCA § 503B(a)(2)(B).

<sup>312</sup> FDA has regulatory authority over facilities that manufacture bulk substances, including foreign facilities, under section 510 of the FDCA. *See generally* Federal Food, Drug, & Cosmetic Act, 21 U.S.C. § 355 *et seq.* (2010).

<sup>313</sup> DQSA, tit. I, § 102; FDCA § 503B(a)(2)(D).

<sup>314</sup> DQSA, tit. I, § 102; FDCA § 503B(a)(8).

<sup>315</sup> DQSA, tit. I, § 102; FDCA § 503B(a)(8).

<sup>316</sup> Pontikes, *supra* note 2. The FDA may require a proposed "risk evaluation and mitigation strategy" if it determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks of the drug. 21 U.S.C. § 355-1. REMS will generally include a time frame for assessing the drug at specified intervals after the drug obtains FDA approval, communication plans with health care providers, and development of patient medication inserts or other education materials. *Id.*; *see also* FDCA § 503B(a)(7).

<sup>317</sup> DQSA, tit. I, § 102; FDCA § 503B(a)(10).

## 2. *Labeling, Good Manufacturing Practices, Reporting Requirements, and Inspections*

Outsourcing facilities must comply with multiple requirements such as the following: 1) displaying detailed information on their labels that helps implement the track and trace provisions and reduces risk of improper use;<sup>318</sup> 2) complying with cGMPs;<sup>319</sup> 3) reporting to the FDA within 15 days of notice all serious and unexpected adverse events associated with their compounded drugs;<sup>320</sup> 4) conducting a prompt investigation of all adverse events associated with their compounded drugs and report the findings to the FDA;<sup>321</sup> 5) maintaining records of correspondences relating to all adverse drug experiences for a period of ten years and allow FDA employees access to the records;<sup>322</sup> and 6) submitting semi-annual reports<sup>323</sup> to the FDA identifying all drugs compounded during the preceding six-month period.<sup>324</sup>

Outsourcing facilities are subject to full inspections pursuant to section 704 of the FDCA.<sup>325</sup> On written notice, the FDA can inspect equipment, finished and unfinished materials, containers, labeling, records, papers, files, processes, controls, and facilities.<sup>326</sup> The FDA will inspect outsourcing facilities on a risk-based schedule according to

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<sup>318</sup> *Id.* The labels of outsourcing facilities' drugs must include: 1) a statement that it is a compounded drug; 2) the name, address, and phone number of the outsourcing facility; 3) the lot or batch number of the drug; 4) the established name of the drug; 5) the quantity or volume of the drug; 6) the date the drug was compounded and the expiration date; 7) instructions for storage and handling; 8) the NDC number, if available; 9) a statement that the compounded drug is "not for resale" and/or for "office use only"; and 10) containers from which individual units of drugs are removed must also include information for adverse event reporting and directions for use. Pontikes, *supra* note 1.

<sup>319</sup> DQSA, tit. I, § 102; FDCA § 503B(a)(10).

<sup>320</sup> DQSA, tit. I, § 102; FDCA § 503B(b)(5); 21 C.F.R. § 310.305 (setting forth the procedure for and scope of adverse event reporting).

<sup>321</sup> 21 C.F.R. § 310.305(c)(1).

<sup>322</sup> *Id.*; *see* 21 C.F.R. § 310.305(f).

<sup>323</sup> DQSA, tit. I, § 102; FDCA § 503B(b). The FDA may grant waivers to the electronic reporting requirement if it finds that "use of electronic means is not reasonable for the person requesting the waiver." *See* FDCA § 503B(b)(3).

<sup>324</sup> DQSA, tit. I, § 102; FDCA § 503B(b)(2). These reports will be due in June and December of each year. DRAFT 503B REGISTRATION GUIDANCE, *supra* note 301. The reports must include: 1) the API and strength of API per unit; 2) the source of the API such as bulk or finished drug; 3) the National Drug Code (NDC) number of the source drug or bulk active ingredient, if available; 4) the dosage form and route of administration; 5) the package description; 6) the number of individual units produced; and 7) the NDC number of the final product, if assigned. *Id.*

<sup>325</sup> Pontikes, *supra* note 1; *see* FDCA § 503B(b)(4); 21 U.S.C. § 374(a) ("Inspection. (a) Right of agents to enter; scope of inspection; notice; promptness; exclusions.").

<sup>326</sup> Pontikes, *supra* note 1.

“known safety risks” in the outsourcing facility, which the FDA determines based on the facility’s compliance, recall, and inspection history, and based on whether the facility intends to compound drugs on the FDA’s drug shortage list and on other criteria.<sup>327</sup>

### 3. *Traditional Compounding*

The revised FDCA section 503A regulates traditional compounding.<sup>328</sup> It also exempts from the NDA approval process certain compounded drugs that include adequate directions for use, and that conform to the FDCA’s general labeling and cGMP requirements.<sup>329</sup> In doing so, the CQA removes the option that the FDA, in theory, had to deem compounded drugs to be “new drugs” that must meet the same standards that apply to manufactures who seek to market new products.<sup>330</sup> The CQA also deletes the provision of section 503A that the Court held unconstitutional in *Western States*.<sup>331</sup>

Section 503A allows pharmacies to compound a drug “for an identified individual patient based on the unsolicited receipt of a valid prescription”<sup>332</sup> and a limited amount (undefined) of drugs before receiving a prescription, if based on historical ordering patterns.<sup>333</sup> Permitted anticipatory compounding includes the preparation of syringes used in the operating room, epidurals, narcotic infusions, diluted and concentrated medications that are not commercially available, and medications unavailable due to supply shortages.<sup>334</sup>

Section 503A prohibits compounding drugs that the FDA has found unsafe or ineffective and withdrawn from the market,<sup>335</sup> or that the FDA has determined are difficult to compound.<sup>336</sup> It also prohibits routine

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<sup>327</sup> Pontikes, *supra* note 1.

<sup>328</sup> Pontikes, *supra* note 1.

<sup>329</sup> FDCA § 503A(a).

<sup>330</sup> Pontikes, *supra* note 1.

<sup>331</sup> FDCA § 503A; DQSA, tit. I, § 102.

<sup>332</sup> FDCA § 503A(a).

<sup>333</sup> FDCA § 503A(a)(2)(A).

<sup>334</sup> Pew Charitable Trusts, American Society of Health-System Pharmacists, and American Hospital Association, Pharmacy Compounding Summit: Summary of a Stakeholder Meeting, at 4 Washington, DC (Feb. 6, 2013).

<sup>335</sup> FDCA § 503A(b)(1)(C). The FDA has already identified nearly sixty drugs it does not allow to be compounded because it does not meet this criterion and it plans to update this list periodically. Pontikes, *supra* note 1.

<sup>336</sup> FDCA § 503A(b)(3)(A).

compounding or compounding inordinate amounts of drugs that are “essentially copies” of commercially available products.<sup>337</sup> Such copies do not include drugs that have undergone modification, such as transformation from tablet to liquid to produce an alternative for an individual patient, when the prescribing practitioner determines that the modification produces a significant benefit for the patient.<sup>338</sup>

Section 503A establishes requirements regarding compounding ingredients. Compounders must use bulk substances bearing valid certificates of analyses for purity and comply with USP or NF monographs on pharmacy compounding. If no monograph exists, then they must use bulk substances that are components of FDA-approved drugs or that appear on an FDA-approved list and manufactured by an FDA-registered facility.<sup>339</sup> In addition, ingredients must meet standards of applicable USP or NF monographs and the USP Chapters on pharmacy compounding if ingredients are not bulk substances.<sup>340</sup>

Section 704(a) of the FDCA exempts pharmacies that do not engage in outsourcing activities from records inspection and registration requirements,<sup>341</sup> if they comply with local pharmacy and medicine regulations, regularly dispense drugs upon prescriptions of practitioners, and only manufacture or distribute drugs for sale in their retail business.<sup>342</sup>

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<sup>337</sup> FDCA § 503A(b)(1)(D). “Essentially copies” are defined differently under section 503A and section 503B. Section 503B defines essentially copies as: 1) a drug that is identical or nearly identical to an FDA-approved drug or a marketed drug not subject to premarket approval unless, in the case of an approved drug, the drug appears on an FDA-created drug shortage list in effect at the time of compounding, distribution, and dispensing; or 2) a drug, a component of which is a bulk drug substance that is a component of an approved drug, unless a change in the drug produces a clinical difference for an individual patient. *See* FDCA § 503B(d)(2).

<sup>338</sup> *Id.*; Pontikes, *supra* note 1, at 20.

<sup>339</sup> FDCA § 503A(b)(1)(A)(i). In its Draft 503A Guidance, the FDA has taken the position that until a bulk substances drug list is published, compounded human drug products should be restricted to bulk substances that are components of FDA-approved drugs or the subject of USP or NF monographs. U.S. FOOD AND DRUG ADMIN., ENFORCEMENT POLICY DURING IMPLEMENTATION OF SECTION 503A OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT (Nov. 1998) [hereinafter DRAFT 503A GUIDANCE].

<sup>340</sup> FDCA § 503A(b)(1)(B).

<sup>341</sup> FDCA § 704(a); 21 U.S.C. § 360(g).

<sup>342</sup> FDCA § 704(a). In comparison, the FDA’s 1998 draft Memorandum of Understanding (MOU), issued to implement the FDAMA, set a twenty percent maximum limit for interstate dispensing and distribution of compounded drugs. *See* Pontikes, *supra* note 1.

#### 4. Federal and State Coordination and Communication

Under the revised Section 503A, the states continue to license and regulate pharmacies, and have primary jurisdiction over them.<sup>343</sup> However, the FDA maintains that compounded drugs are also subject to the FDCA unless specifically exempted.<sup>344</sup> The FDA intends to enforce FDCA sections 501 and 502 which prohibit drugs that: 1) consist of filthy, putrid, or decomposed substances; 2) are prepared under unsanitary conditions; 3) differ in quality and purity from the recognized official compendium with which the drug purports to comply; or 4) are not packaged or labeled as set forth in the official compendium in which the drug purports to comply.<sup>345</sup>

Section 503A also requires the FDA to consult with the NABP and develop a Memorandum of Understanding (MOU) with the states,<sup>346</sup> in order to respond to the interstate distribution of “inordinate amounts” of compounded drugs and facilitate state investigation of complaints concerning interstate distribution.<sup>347</sup> The FDA’s 2015 draft MOU<sup>348</sup> specified that if the states do not enter into the final MOU, section 503A will prevent the distribution of compounds in excess of five percent of the total prescription orders dispensed or distributed.<sup>349</sup>

Section 105 of the CQA is intended to improve the communication between the State Boards of Pharmacy and the FDA.<sup>350</sup> The statute requires that the reporting mechanism be implemented in consultation with the NABP.<sup>351</sup> The State Boards of Pharmacy must notify the FDA when

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<sup>343</sup> U.S. FOOD AND DRUG ADMIN., *Compounding and the FDA: Questions & Answers* (Oct. 6, 2015), <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339764.htm>.

<sup>344</sup> U.S. DEP’T OF HEALTH & HUMAN SERVICES, INTERIM POLICY ON COMPOUNDING USING BULK DRUG SUBSTANCES UNDER SECTION 503A OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT, GUIDANCE FOR INDUSTRY at 2 (2017), <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM469120.pdf>.

<sup>345</sup> *Id.* at 6.

<sup>346</sup> FDCA § 503A(3)(B)(i).

<sup>347</sup> *Id.*

<sup>348</sup> Draft Memorandum of Understanding Addressing Certain Distribution of Compounded Human Drug Products Between the State of [insert State] and the U.S. Food and Drug Administration 2015, <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/UCM434233.pdf> (last visited Feb. 26, 2018).

<sup>349</sup> *Id.*; DRAFT 503A GUIDANCE, *supra* note 339; Pontikes, *supra* note 1.

<sup>350</sup> FDA Implementation of the Compounding Quality Act (Sept. 14, 2016). The NECC crisis highlighted the lack of effective communication between State Boards of Pharmacy and the FDA. See Drug Quality Security Act, Hearing on HR3204 before the House (statement of Rep. Henry A. Waxman) (Sept. 28, 2013); Pontikes, *supra* note 1.

<sup>351</sup> Pontikes, *supra* note 1. The FDA is also to consult with the NABP on the creation of this

they: 1) issue a warning letter or impose any sanctions for violations of compounding pharmacy regulations; 2) suspend or revoke a compounding pharmacy license or registration; or 3) learn of any recall regarding the quality or purity of a compounded drug.<sup>352</sup> Moreover, the FDA must immediately notify the State Boards of Pharmacy if the agency determines that a pharmacy violated section 503A or if it receives any notifications from a State Board of Pharmacy for any state related violation.<sup>353</sup>

*B. The Drug Supply Chain Security Act (DSCSA)*

The DSCSA creates track and trace requirements for each package of medication in the pharmaceutical distribution chain as a means to facilitate detection and removal of contaminated or counterfeit products.<sup>354</sup> The legislation outlines a ten-year plan to implement an electronic, interoperable system across the United States.<sup>355</sup> The key provisions include these requirements for manufacturers, repackagers, and wholesalers:<sup>356</sup>

**Product Identification.** Each prescription drug package will have a unique product identifier, such as a bar code, that can be easily read electronically.

**Product Tracing.** All entities will provide information regarding a drug product and any personnel who handled the drug each time the product was sold.

**Product Verification.** All entities will have to establish systems and processes to verify the product identifier on certain prescription drug packages.

**Detection and Response.** All entities will have to quarantine and promptly investigate a drug that has been suspected of being counterfeit, unapproved, or dangerous.

**Notification.** All entities will have to establish processes to notify

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mechanism for enhanced communication between the State Boards of Pharmacy and the FDA. See DQSA, tit. I, § 105.

<sup>352</sup> DQSA, tit. I, § 105(b)(1)-(3).

<sup>353</sup> DQSA, tit. I, § 105(d).

<sup>354</sup> Drug Supply Chain Security Act (DSCSA), <http://www.fda.gov/Drugs/DrugSafety/DrugIntegrityandSupplyChainSecurity/DrugSupplyChainSecurityAct> (last updated Nov. 28, 2017).

<sup>355</sup> See U.S. DEP'T. OF HEALTH & HUMAN SERVICES ET AL., DRUG SUPPLY CHAIN SECURITY ACT IMPLEMENTATION: IDENTIFICATION OF SUSPECT PRODUCT AND NOTIFICATION GUIDANCE FOR INDUSTRY (2016).

<sup>356</sup> *Id.* The act requires manufacturers to serialize drugs by 2017, and mandates the use of an electronic product tracing system by 2023. *Id.*

the FDA and other parties if an illegitimate drug is identified.

Licensing of Wholesalers and Distributors. Wholesale drug distributors will have to report their licensing status and contact information to the FDA which will be made publicly available.

Third-Party Logistics Provider Licensing. Third-party logistic providers, i.e., those who provide storage and logistical operations related to drug distribution, will have to obtain a state or federal license.

### *VIII. Key Unresolved Issues*

#### *A. The Legal Status of Compounding Pharmacies Under Federal Law*

The legal status of non-traditional compounding and outsourcing facilities remains unresolved. The plain language of the FDCA favors the interpretation that the FDA has authority over drug compounding if compounded drugs constitute new drugs.<sup>357</sup> Specifically, the FDCA states that no person can “introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application [is] filed” with the FDA pursuant to the statute with respect to the drug.<sup>358</sup> However, the legislative history of the FDCA supports the view that manufacturers were the intended target of the 1938 Act, not traditional compounding pharmacies.<sup>359</sup> Therefore, it is unclear whether the FDCA deems certain “traditional” compounding unlawful.<sup>360</sup>

The FDA has declined to test the current limits of federal authority to regulate “traditional” compounding, and deferred to state governments for compounding regulation.<sup>361</sup> As a result, the limits of the FDA’s authority over drug compounding remains uncertain.<sup>362</sup> Courts might not support new FDA regulation of traditional compounding.

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<sup>357</sup> *Hartford Underwriters Ins. Co. v. Union Planters Bank, N.A.*, 530 U.S. 1, 6 (2000). If a statute’s terms are “plain,” the Supreme Court has noted that a court should look no further and enforce the law “according to its terms.” *See id.* (citations omitted); CRS REPORT R43038, *supra* note 44, at 11.

<sup>358</sup> 21 U.S.C. § 355(a).

<sup>359</sup> *United States v. Franck’s Lab, Inc.*, 816 F. Supp. 2d 1209, 1245-46 (M.D. Fla. 2011).

<sup>360</sup> *Id.* at 1239.

<sup>361</sup> CPG § 460.200 (May 29, 2002); CPG § 608.400 (July 14, 2003); CRS REPORT R43038, *supra* note 44, at 12.

<sup>362</sup> This lack of resolution burdens “traditional” compounders, whose conduct could be in violation of federal law. *Med. Ctr. Pharmacy v. Mukasey*, 536 F.3d 383, 399-400 (5th Cir. 2008). As one court noted, “it remains no small burden for compounding pharmacists . . . to ‘live in sin,’ [as] their livelihood [has] no greater assurance than the FDA’s good graces.” *Id.*

However, Congress could expand the scope of the FDCA to reach “traditional” compounding.<sup>363</sup>

In addition, the CQA does not authorize the FDA to regulate compounding pharmacies unless such pharmacies voluntarily register as outsourcing pharmacies and accept FDA oversight. Therefore, the new regulatory controls can work only if compounding pharmacies register and accept to work under the new regulatory system. Proponents of the voluntary system argue that market forces will cause larger compounders to register because hospitals and other providers will choose to do business with compounders subject to FDA quality standards, inspection requirements, and adverse event reporting. It remains to be seen how many large compounders will register and whether state regulatory agencies will improve facility inspections and share information.

*B. Conflicting Standards within Federal Law and Between Federal and State Law*

Outsourcing pharmacies, including federal and state-licensed compounding pharmacies, all compound and repackage drugs based on individualized prescriptions. However, the CQA applies different standards regarding labeling, quality, and adverse event reporting for facilities depending on whether they are outsourcing facilities, state-licensed or federally regulated. The DQSA’s definition of an outsourcing facility includes only facilities engaged in the compounding of “sterile” drug products. However, the FDCA’s definition of compounding applies to all drugs in general.<sup>364</sup>

The DQSA standards do not apply to 503A entities, such as traditional drug compounding pharmacies, and are not imposed consistently across all jurisdictions.<sup>365</sup> Yet, the DQSA standards apply to section 503B entities, i.e., outsourcing facilities, which are federally regulated. However, the DQSA does not make clear what responsibility states bear

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<sup>363</sup> *Gonzales v. Raich*, 545 U.S. 1, 22 (2005) (holding that the authority under the Commerce Clause extends such that Congress can regulate activities when, taken in the aggregate, substantially affect interstate commerce); see CRS REPORT R43038, *supra* note 44, at 12.

<sup>364</sup> See generally Drug Quality and Service Act (DQSA). In addition, the DQSA applies only to “human drugs” and not to drugs for animal use. *Id.*

<sup>365</sup> U.S. FOOD AND DRUG ADMIN, FDA GUIDANCE, ADVERSE EVENT REPORTING FOR OUTSOURCING FACILITIES UNDER SECTION 503B OF THE FEDERAL FOOD, DRUG AND COSMETIC ACT (2015), <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm434188.pdf>.

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vis-à-vis outsourcing facilities, and the FDA has yet to clarify the relation between federal and state standards for outsourcing facilities. Furthermore, some states do not recognize federally regulated outsourcing facilities and require that such facilities be licensed by the State Boards of Pharmacy as a pharmacy or pharmaceutical distributor. Some states argue that outsourcing facilities must meet both federal and state standards because they can make medications, compound drugs, and market them around the country similar to a manufacturer, but also be engaged in filling prescriptions similar to a pharmacist.

It is unclear whether federal legislation will permit non-traditional compounding practices to thrive outside of the outsourcing facility category. If it does, the CQA will not have effectively addressed the problems that caused the NECC crisis, despite the FDA's best efforts.